The role of surgery in the management of oesophageal cancer
An assessment of staging and multi-modality treatment over ten years

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Title

The role of surgery in the management of oesophageal cancer : An assessment of staging and multi-modality treatment over ten years

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Abstract

Introduction : Oesophageal cancer represents a formidable challenge to both patients and clinicians. Due to its propensity for early systemic dissemination, the majority of patients are not eligible for curative treatment. In the minority of patients suitable for surgical resection, there remain many controversies in management. Good prospective data from high volume centres is vital in attempting to improve staging algorithms and management strategies.

Methods : A large prospectively collected database was utilised, the result of a research collaboration between two high volume oesophageal cancer centres (St Thomas' hospital and Royal Marsden hospital) in London, UK. The database consisted of consecutive patients undergoing surgery for oesophageal or oesophago-gastric junction (type 1 and 2) tumours between 2000 and 2010. The database was rigorously cross-referenced to ensure accuracy. Data were analysed independently at an aligned academic unit by an experienced bio-statistician. The aim was to assess factors predicting early recurrence and death after oesophagectomy (study 1), the influence of surgical radicality on outcomes (study 2), and the down-staging effects of neo-adjuvant chemotherapy (study 3). Each of these was to be presented as a scientific article, accepted for peer-review publication.

Results : Of the 680 patients included, the median age was 64 years with a male preponderance (81%). The majority of patients had adenocarcinoma (82%), although patients with squamous cell carcinoma (14%) and high grade dysplasia (4%) were also included in the database. Multivariable analysis showed T and N stage (T3-4 N2-3 OR 10.6; 95% CI 2.8-40.0), poor differentiation (OR 2.8; 95% CI 1.4-5.5), involved resection margins (OR 2.7; 95% CI 1.2-6.0) and poor response to pre-operative chemotherapy (OR 3.2; 95% CI 1.1-8.8) to independently predict early recurrence and

death after surgery. The predominant mode of recurrence was with distant metastases. Surgical approach, comparing transhiatal with transthoracic oesophagectomy, had no impact on overall survival (HR 1.07, 95% CI 0.84 – 1.36) or tumour recurrence (HR 0.99, 95% CI 0.76 – 1.29) when adjusted for potential confounding factors. In patients undergoing neo-adjuvant chemotherapy, outcome was determined by tumour stage after chemotherapy rather than that of initial presentation. This may have a significant impact on staging algorithms with a shift in focus to assessment of tumour stage after chemotherapy in order to improve clinical decision making and predict outcome. The three studies were published in the Journal of Surgical Oncology, British Journal of Surgery and Journal of Clinical Oncology respectively.

Conclusions : Predictive models that could guide individualised patient management are achievable. These could include selecting patients for specific neo-adjuvant treatment strategies, guiding surgical approach in patients deemed suitable for resection and improved selection of patients who are most likely to benefit from surgery.

List of publications

Factors associated with early recurrence and death after esophagectomy for cancer

Andrew R Davies, Andrew Pillai, Pranab Sinha, Harinderjeet Sandhu, Amina Adeniran, Fredrik Mattsson, Asif Choudhury, Matthew J Forshaw, James A Gossage, Jesper Lagergren, William H Allum, Robert C Mason

Journal of Surgical oncology 2014;109:459–464

Surgical resection strategy and the influence of radicality on outcomes in oesophageal cancer

A. R. Davies, H. Sandhu, A. Pillai, P. Sinha, F. Mattsson, M. J. Forshaw, J. A. Gossage, J. Lagergren, W. H. Allum and R. C. Mason

British Journal of Surgery 2014; 101: 511–517

Tumor stage after neo-adjuvant chemotherapy determines survival after surgery for adenocarcinoma of the esophagus and esophago-gastric junction

Andrew R. Davies, James A. Gossage, Janine Zylstra, Fredrik Mattsson, Jesper Lagergren, Nick Maisey, Elizabeth C. Smyth, David Cunningham, William H. Allum, Robert C. Mason

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Figures

Abbreviations

AC	Adenocarcinoma
AJCC	American Joint Committee on Cancer
AUC	Area under the curve
AURKA	Aurora kinase receptor
CF	Cisplatin & 5 fluorouracil
CI	Confidence interval
COX	Cyclo-oxygenase
CPR	Complete pathological response
CRM	Circumferential resection margin
CRP	C-reactive protein
CRT	Chemo-radiotherapy
CT	Computed tomography
DFS	Disease free survival
ECF	Epirubicin, cisplatin & 5 fluorouracil
ECX	Epirubicin, cisplatin & capecitabine
EGFR	Epidermal Growth Factor
EMR	Endoscopic mucosal resection
ERD	Early recurrence & death
ESD	Endoscopic sub-mucosal dissection
EUS	Endoscopic ultrasound
FDG	Fluoro-deoxy-glucose
GI	Gastro-intestinal
GORD	Gastro-oesophageal reflux disease
GP	General Practitioner
Hb	Haemoglobin
HER	Human epidermal growth factor receptor
HGD	High grade dysplasia
LN	lymph node
LTA	Left thoraco-abdominal oesophagectomy
LTS	Long term survival
MDT	Multi-disciplinary team
MRI	Magnetic resonance imaging
MTRG	Mandard tumour regression grade
MTV	Mean tumour volume
NAC	Neo-adjuvant chemotherapy
NACRT	Neo-adjuvant chemo-radiotherapy

NPV	Negative predictive value
OGJ	Oesophago-gastric junction
OR	Odds ratio
OS	Overall survival
PET	Positron emission tomography
PPV	Positive predictive value
QOL	Quality of life
RCP	Royal College of Pathologists, UK
RCT	Randomised controlled trial
SCC	Squamous cell carcinoma
STIR TSE	Short inversion time inversion-recovery turbo spin-echo
SUV	Standardised uptake variable
THO	Transhiatal oesophagectomy
TLG	Total lesion glycolysis
TTO	Transthoracic oesophagectomy
UK	United Kingdom
US	United States of America
VEGF	Vascular Endothelial Growth Factor

Declaration

The content of this thesis is my own work. Whilst any scientific paper involves contributions from other authors, I am the first author of all three manuscripts, responsible for the design of the studies, data presented within them and discussion content. Further contributions are acknowledged within the thesis.

Acknowledgements

I would like to express a huge gratitude to my two supervisors. Professor Robert Mason, who inspired me to pursue a career in oesophageal cancer surgery, and whose skill and dedication are largely responsible for the excellent set of results presented in this thesis. Professor Jesper Lagergren who helped develop my research skills; to appreciate the attention to detail and the support network required to take surgical research into high ranking clinical journals. To both supervisors, my appreciation for the many hours of support given to the completion of this thesis.

To an outstanding team of colleagues at St Thomas', particularly James Gossage and Janine Zylstra, for their expertise and on-going efforts. Fredrik Mattsson whose phenomenal statistical knowledge and keen sense of scientific rigour gave me many sleepless nights, but infinitely strengthened the manuscripts contained within this thesis

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South West trains, responsible for endless delays whilst commuting to work, which inadvertently allowed me the time to complete this thesis. Finally, to my wife Sophie and two children Amelie and Freddie, for their un-ending support. You can have the computer back now !

1. Introduction

1.1 Oesophageal cancer

1.1.1 Background on oesophageal cancer

Oesophageal cancer represents a formidable challenge to both patients and clinicians. It is the eighth most common cancer worldwide and the sixth most common cause of cancer death in the UK [1]. Each year over 8,000 patients are diagnosed with oesophageal cancer in the UK which has a particularly high incidence of adenocarcinoma of the oesophagus [2]. It is a cancer with a propensity for early systemic dissemination aligned with a late onset of symptoms that often leads to delayed diagnosis. As a result, the majority of patients will not be eligible for curative treatment. The overall survival of patients diagnosed with oesophageal cancer in the UK between 2005 and 2009 was 13% at 5 years [2]. Even in those patients with resectable tumours, historical series have rarely shown five year survival to exceed 25% [3, 4].

1.1.2 Improvement in outcomes and centralisation of services

Some cause for optimism lies in the recent advances in the staging and management of these tumours, including the widespread adoption of peri-operative oncological therapies. A number of cohort studies from specialist centres have shown improved five year survival with such strategies, reaching 50% in some published studies following surgery [5, 6]. Centralisation of services in the UK, and elsewhere, has been shown to improve survival [7-9] and reduce post-operative mortality [10, 11]. This has almost certainly contributed to the significant reduction in UK National audit mortality rates between 2000 and 2013, decreasing from 10% to 3% [12]. The concentration of resources into high volume centres has led to the development of specialist multi-disciplinary teams (MDT) with a pooled expertise in radiology, oncology, anaesthesia, critical care and surgery amongst others. This MDT approach has also been shown to improve staging accuracy as well as decision making [13].

1.1.3 Classification and aetiology of Oesophageal cancer

There is a significant geographical variation in the histological sub-type of oesophageal cancer. In the western world, the incidence of adenocarcinoma (AC) of the lower oesophagus and oesophago-gastric junction (OGJ) is increasing and has overtaken that of squamous cell carcinoma (SCC) [14, 15]. In south-east Asia, SCC remains the most prevalent and AC is rare. Risk factors for the development of SCC are tobacco smoking, alcohol excess, achalasia and genetic mutations amongst others [16, 17]. Barrett's oesophagus, a pre-malignant condition caused by gastro-oesophageal reflux disease (GORD) is strongly associated with the development of adenocarcinoma [18-20]. Although arguably part of the same causal pathway, reflux, obesity, male sex, hiatus hernia and smoking are also associated with the development of adenocarcinoma.

Tumours of the oesophago-gastric junction (OGJ) may be categorised according to their location relative to the true junction. The classification originally described by Siewert is most commonly used [21]. For the purposes of this thesis, oesophageal cancer refers to tumours of the oesophagus and OGJ (Siewert types 1 and 2). This grouping has been accepted as part of TNM 7, although there is particular controversy regarding type 2 tumours and whether they should be considered as oesophageal cancers, gastric cancers or a separate entity in their own right.

Whilst AC and SCC sub-types share a common anatomical location i.e. the oesophagus, there is convincing evidence that they should be considered as distinct pathological entities by virtue of their differing aetiology, natural history and sensitivity to oncological therapies [22-25].

Squamous carcinoma affects the native oesophageal squamous mucosa and by definition includes tumours of the proximal, mid and distal oesophagus. Adenocarcinomas, tend to arise from the glandular mucosa of the true OGJ or from a segment of Barrett's oesophagus. As such these tumours are almost exclusively found in the lower oesophagus and OGJ. The pattern of dissemination may also be different with adenocarcinomas having a higher propensity for metastatic spread compared to squamous carcinomas which more frequently affect the mediastinal and cervical lymph nodes [23-27]. Finally, SCC is more sensitive to the effects of radiotherapy, hence the widespread use of definitive CRT in the treatment of proximal and mid oesophageal SCCs in the UK [28, 29]. The treatment of lower oesophageal SCC is more contentious and will be discussed later in this chapter.

1.1.4 Known Prognostic factors in oesophageal cancer

Tumour stage – The most significant prognostic marker in oesophageal cancer is tumour stage, with more advanced tumours carrying a worse prognosis. The TNM staging classification is widely accepted, currently in its 7th edition. The AJCC classification further categorises tumours into stage-matched groups (I-IV) according to prognosis [30].

A larger tumour, reflected by higher T stage, has a greater risk of lymph node metastases and in turn a higher probability of distant metastatic disease [31-34]. This stepwise progression of disease from primary tumour to lymph node metastasis to systemic disease has been widely acknowledged, however it is not a pre-requisite. Some patients are found to have systemic disease in the absence of lymphadenopathy and a further group may experience "skip" lymph node metastases. Local infiltration into structures such as the aorta or bronchi (T4 disease) can render a tumour unresectable. The natural history of inoperable oesophageal cancer from diagnosis to death is seldom greater than 12 months.

In compiling the 7th edition TNM staging system, N status was re-classified according to the number of lymph node metastases (**N0** – no lymph nodes involved, **N1** : 1-2 LNs, **N2** : 3-6 LNs, **N3** >6 LNs). A number of studies have demonstrated that above a certain number of positive lymph nodes (range 3-8 lymph nodes) the likelihood of underlying systemic disease approaches 100%, and hence these patients are rarely cured by surgery [32]. Other studies have examined the ratio of involved LNs to total number resected, concluding that this ratio is a significant marker of prognosis [35]. Regardless of the method by which it is defined, nodal status is arguably the most influential prognostic factor in patients undergoing surgery for oesophageal cancer.

The presence of metastatic disease (haematogenous or peritoneal metastases and distant lymph node metastases) precludes a radical treatment pathway. Although other GI cancers, most notably colorectal carcinomas, are now considered for surgery in the presence of such metastases, particularly in the liver, the very poor prognosis of oesophageal cancer and the magnitude of the surgery, make this option unappealing [36]. However, some case series have reported reasonable survival in highly selected cases [37].

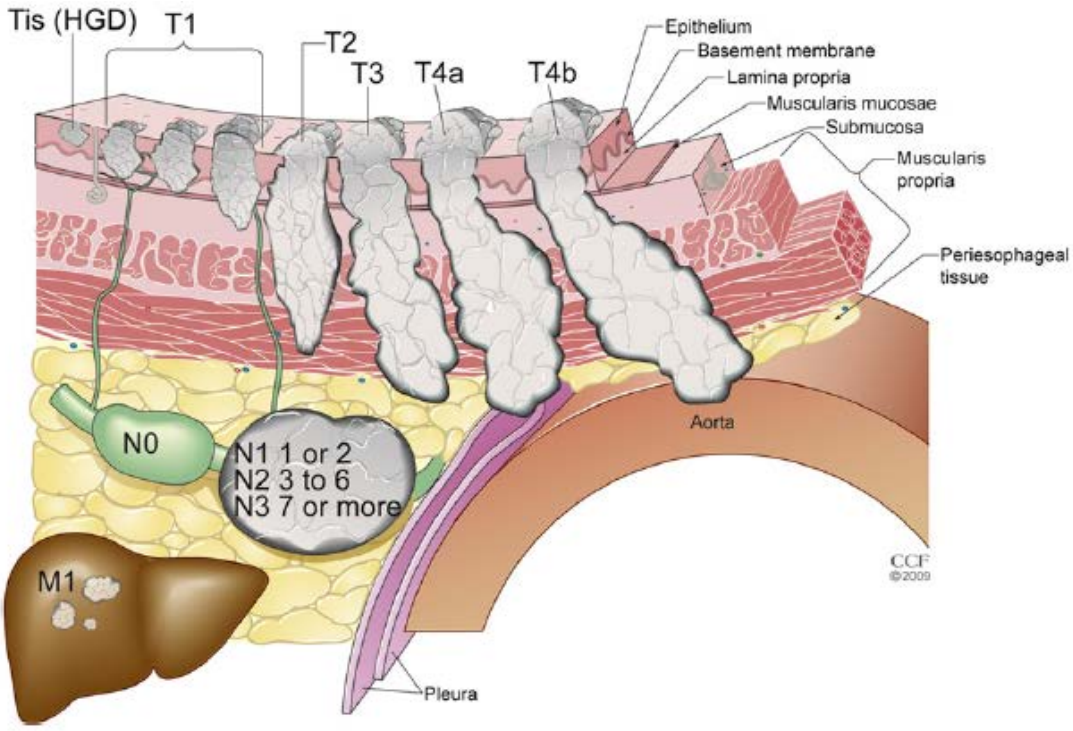

Fig. 1 *Seventh edition TNM classifications. T is classified as Tis: high-grade dysplasia; T1: cancer invades lamina propria, muscularis mucosae, or submucosa; T2: cancer invades into but not beyond the muscularis propria; T3: cancer invades the para-oesophageal tissue, but does not invade adjacent structures; T4a: resectable cancer invades adjacent structures,such as pleura, pericardium, or diaphragm; and T4b: unresectable cancer invades other adjacent structures, such as aorta, vertebral body, or trachea. N is classified as N0: no regional lymph node metastasis; N1: regional lymph node metastases involving 1 to 2 nodes; N2: regional lymph node metastases involving 3 to 6 nodes; and N3: regional lymph node metastases involving 7 or more nodes. M is classified as M0: no distant metastasis; and M1: distant metastasis [38]. (Reprinted with permission, Cleveland Clinic Centre for Medical Art & Photography 2001–2012. All Rights Reserved.)*

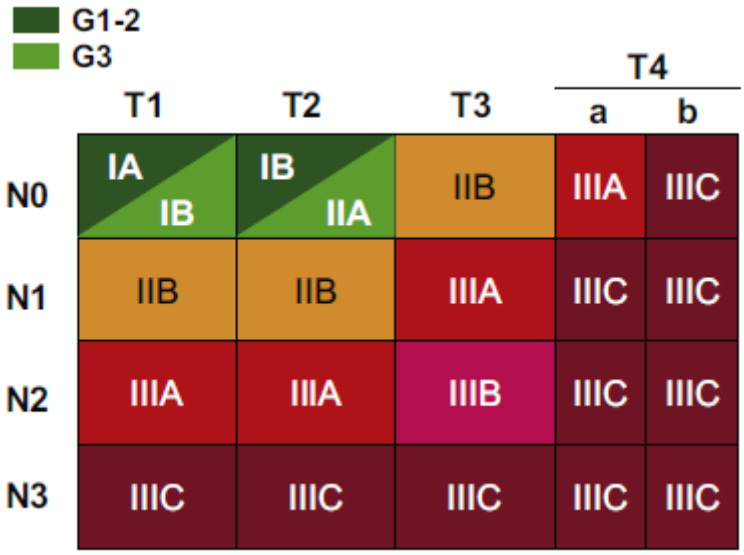

Fig. 2 *Stage groupings for M0 adenocarcinoma by T and N classification and histologic grade (G) [38]. (Reprinted with permission Cleveland Clinic Centre for Medical Art & Photography 2001–2012. All Rights Reserved)*

Tumour grade - The measure of tumour differentiation (well, moderately, poorly or un-differentiated) has been shown in numerous studies to affect prognosis [34]. Poorly differentiated tumours are more unstable, increasing the likelihood of metastases. Additionally, the cell populations within a poorly differentiated tumour may be more heterogeneous, making them less likely to respond to generic systemic therapies.

Lymphovascular invasion - The ability of a tumour to invade blood vessels, lymphatics and nerves determines its ability to metastasise. It is not surprising, therefore, that lympho-vascular invasion at a microscopic level is associated with poor prognosis.

Completeness of resection (R0/1/2) - Incomplete surgical resection, with microscopic (R1) or macroscopic (R2) margin involvement is associated with poor prognosis [39]. In oesophageal cancer, the circumferential margin (CRM) is particularly

vulnerable due to the absence of a serosal layer in the oesophagus, and the minimal volume of peri-oesophageal fat to separate the tumour from adjacent structures. Longitudinal margin involvement is rare, and seldom the cause of death, as these patients generally die of metastatic disease [40]. Although CRM involvement is directly related to tumour T stage (and by association, therefore, a higher risk of lymph node involvement), an R1 resection has been shown to be an adverse prognostic marker in numerous studies that have adjusted for such confounders [41, 42].

Circumferential margin involvement, in the UK, is defined by the Royal College of Pathologists criteria of tumour cells at or within 1mm of the resected margin [43]. However, in the USA, the definition is tumour present at the margin thus making the CRM rates inherently lower [30]. There is considerable controversy as to which definition is superior [44, 45]. Undoubtedly, the presence of tumour at the margin is associated with the worst prognosis [39]. However, it has also been shown that the intermediate group (tumour cells within 1mm but not at the margin) have a worse prognosis than patients with a margin greater than 1mm [42]. This has potentially important implications, as it could influence peri-operative treatment strategies, such as the use of radiation. It also makes the comparison of surgical series utilising different definitions of margin involvement difficult to interpret.

Mandard tumour regression grade (MTRG) - Evidence of tumour response to chemoradiotherapy, as described initially by Mandard, has been shown to have significant prognostic value in oesophageal cancer [46]. Mandard tumour regression grade (MTRG) is a categorical scale between 1 (complete response) and 5 (no response) for the objective measurement of pathological response in samples of the primary tumour. MTRG has become a standard component of the reporting of oesophageal resection specimens in the UK, despite the fact that the score was

originally described for CRT rather than the widely practised chemotherapy. Nonetheless, numerous studies have supported its use and whilst other TRG's have been proposed, none have superseded Mandard [47-49]. Some studies have utilised 3 groups as opposed to 5 (MTRG 1, MTRG 2&3, MTRG 4&5). A further study that analysed survival and MTRG suggested that M3 naturally aligns with M4&5, and thus only patients exhibiting a significant response to NAC (<10% viable tumour) gain a survival advantage [50]. In this study the authors also assessed the relative importance of pathological response in the primary tumour to down-staging in regional lymph nodes. They demonstrated that 26% of patients had evidence of significant response in the primary tumour following NAC (MTRG 1&2), but when lymph node down-staging was also included, the total number of responders increased to 48%. The lymph node responders experienced improved disease free survival (DFS) compared to the non-responders, irrespective of the Mandard score in the primary tumour. One explanation for this finding was that the smaller population of tumour cells within a lymph node may be more susceptible to the effects of chemotherapy, compared to the larger primary tumour. This study has potentially important implications both in terms of assessing lymph node response after NAC with staging modalities and also in the selection of patients who might benefit from adjuvant treatment, a subject which remains controversial.

Acute phase proteins (Albumin / CRP) - There has been significant interest in the use of acute phase proteins as predictors of poor outcome in oesophageal cancer. A number of studies have suggested a low albumin and high CRP are associated with poor survival, although the exact mechanisms are unclear [51, 52]. It has been proposed that an aggressive, biologically active tumour may induce an acute phase response. Albumin may also fall in patients who are nutritionally compromised, and whilst the role of albumin as a marker of nutrition has been challenged, poor oral intake and significant weight loss have been shown to have a negative impact on survival [53].

Biological markers (EGFR, VEGF, HER) - A number of receptors are over-expressed in oesophageal cancer including those belonging to the EGFR family (EGFR, HER1,2,3), VEGF and Aurora kinases (AURKA). EGFR may be overexpressed in 30-70% of oesophageal cancers [54-56], HER-2 in 19-43% [57] and VEGF in 30-60% [58], all associated with poor outcome. The prognostic role of these receptors and others such as E-cadherin and COX-2 has been reported in a number of meta-analyses [59-63].

Gene signatures - Gene expression profiling has allowed for the correlation of gene signatures with clinical and pathological outcomes in oesophageal cancer. One UK study demonstrated a 4 gene signature to strongly correlate with survival (p=0.0001) and this was independently prognostic in a multivariable model that adjusted for other known confounding factors (p=0.013) [64]. A further study from the US reported very similar outcomes albeit with the use of a different gene signature [65].

1.2 Staging of oesophageal cancer

The traditional diagnosis and staging of oesophageal cancer utilised endoscopy with biopsy and computed tomography (CT) to identify patients suitable for surgical resection. This approach often under-estimated the true extent of disease and, as a result, a significant proportion of patients underwent “exploratory” open and close surgery [66]. Improvements in technology, specifically the introduction of multi-detector CT, have enabled imaging at much higher spatial and temporal resolutions. As a result the sensitivity of CT has improved, with a meta-analysis of 20 studies suggesting 59% sensitivity for nodal status [67] and other studies quoting 37-66% for metastatic disease [68-70]. However, CT still struggles to accurately stage the primary tumour (T stage), has low discriminatory power for nodules below 1cm in diameter, and is poor at predicting response to neo-adjuvant chemotherapy [71, 72] .

Additional staging modalities have emerged to compliment CT by providing a more detailed assessment of the primary tumour and surrounding lymph nodes. Endoscopic ultrasound (EUS) is more accurate than CT in assessing T stage and N status, the former because of its ability to delineate the layers of the oesophageal wall [38]. A meta-analysis incorporating 2558 patients from 49 studies demonstrated EUS to have a sensitivity and specificity of 81% and 99% respectively for T1 disease, 81% and 96% for T2, 91% and 94% for T3 and 92% and 97% for T4 disease [73]. It can identify contact between the primary tumour and adjacent structures such as the trachea, aorta, pericardium or diaphragm and in doing so provide important information regarding resectability. A tumour length of greater than 5 cm on EUS, predicts T3 (or greater) disease with sensitivity, specificity, PPV and NPV of 89%, 92%, 89% and 92% respectively [74]. For early tumours, EUS may identify patients suitable for endoscopic resection. However, it struggles to distinguish Tis from T1a/b disease and hence EMR

continues to have an important diagnostic role to play in the selection of these patients for surgery, by providing a histological specimen for analysis [75].

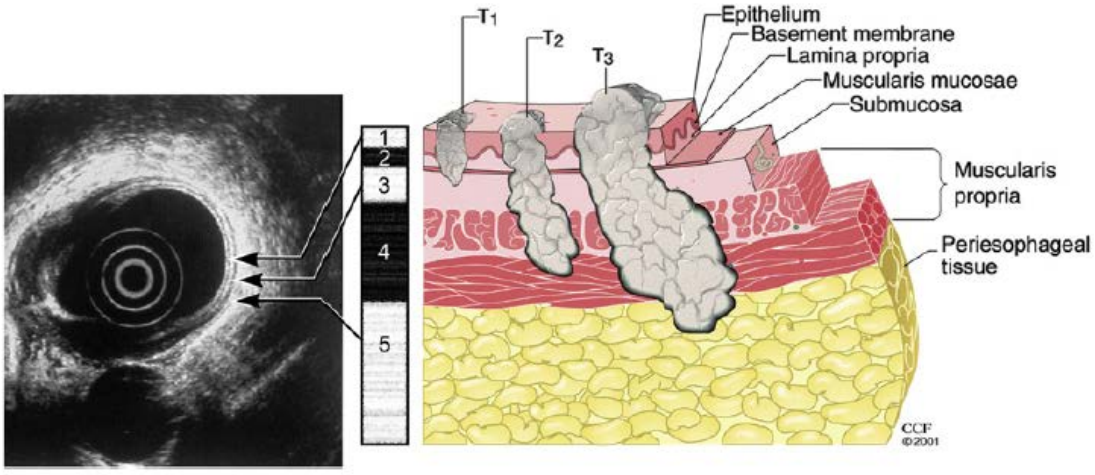

Fig. 3 *The oesophageal wall is visualized as 5 alternating layers of differing echogenicity by EUS. The first layer is hyperechoic (white) and represents the superficial mucosa (epithelium and lamina propria). The second layer is hypoechoic (black) and represents the deep mucosa (muscularis mucosa). The third layer is hyperechoic and represents the submucosa. The fourth ultrasound layer is hypoechoic and represents the muscularis mucosa. This layer (muscularis propria) is critical in differentiating T1, T2, and T3 cancers. The fifth ultrasound layer is hyperechoic and represents the peri-oesophageal tissue. The thickness of the EUS layers is not equal to the thickness of anatomic layers[38]. (Reprinted with permission, Cleveland Clinic Centre for Medical Art & Photography 2001–2012. All Rights Reserved.)*

Other original studies and meta-analyses have shown the sensitivity and specificity of EUS for N stage may exceed 80% [67, 73, 76]. This may be further improved by the use of fine needle aspiration (FNA), reaching 96% in one study [73]. EUS can also assess the number of regional lymph nodes (LNs) in line with the requirements of the TNM 7 classification, and this predicts survival [77-79]. As with any dynamic investigation, EUS is subject to inter-observer variation, although accuracy is improved when performed by endoscopists in high volume centres [80]. Additionally it may not be possible in patients with stenotic tumours, with one study suggesting that this occurred in 6% of patients and was sub-optimal in a further 14% [72]. Such strictures, however, are highly predictive of advanced disease [74, 81].

The introduction of Positron emission tomography (PET) imaging has attracted significant interest as it provides a biological assessment of the tumour based on the uptake of fluoro-deoxy-glugose (FDG). PET has an improved sensitivity for metastatic disease and has been shown to up-stage 15% of patients to M1 disease who were previously being considered for radical treatment [82-84]. A meta-analysis of PET imaging demonstrated a sensitivity of 67% and specificity of 97% for metastatic disease although the yield for lesions below 1cm in diameter was poor [85]. Other studies have shown even more impressive results for PET at detecting metastases (sensitivity, specificity and accuracy of 88%, 93% and 91% respectively). PET appears to be better than CT for assessing distant metastases, in one study correctly up-staging 62% of the patients with metastases who had previously undergone a (false) negative CT scan [69]. All of the metastases missed by PET were less than 1cm.

The development of PET/CT with its ability to correlate anatomical and functional tumour characteristics has further improved staging accuracy, such that it is now considered more accurate than CT at staging the local tumour [86] and distant metastases [68, 87]. One limitation in the early experience of PET imaging was that uptake in the primary tumour obscured local lymph nodes [88, 89]. Whilst EUS was said to provide a more accurate nodal assessment in this scenario, modern PET/CT has somewhat mitigated this problem [89]. A meta-analysis of PET imaging in the assessment of N stage has shown sensitivity and specificity of 59% and 81% respectively [67]. A recent study has demonstrated nodal disease on PET/CT at diagnosis to be a significant adverse prognostic marker [90].

Numerous biological parameters measurable by PET have been reported as prognostic in oesophageal cancer. These include standardised uptake variable (SUV), mean tumour volume (MTV), total lesion glycolysis (TLG) and tumour heterogeneity [91].

Metabolic uptake has been shown to differ significantly between AC and SCC [83]. Recent interest has also focussed on the measurement of tumour heterogeneity on PET as a surrogate for aggressive tumour biology and response to chemotherapy [92].

As a result of these promising results, PET/CT has been widely adopted in the UK in the initial assessment of oesophageal cancer, and in some centres, in the re-staging of tumours following chemotherapy.

The role of staging laparoscopy is somewhat controversial. Studies have suggested that the addition of laparoscopy changes management in 10% of patients (2% who were initially over-staged and therefore could proceed to surgery, 8% with previously undetected M1 disease [93]. Others have suggested sensitivities for liver and peritoneal disease of 86% and 71% respectively, concluding that laparoscopy may change management in as many as 17% of patients [94]. It is currently recommended for gastric and junctional carcinomas, but not for primary oesophageal carcinomas, based on the likelihood of metastatic disease below the diaphragm. However, it has been argued that the improved sensitivity of modern multi-slice CT and the addition of PET, may nullify the additional benefit of staging laparoscopy. Given the requirement for general anaesthetic, as well as the associated risks of laparoscopic surgery, its role in oesophageal carcinomas remains limited to selected patients.

Magnetic resonance imaging (MRI) has attracted significant interest due to its improved soft tissue resolution compared to CT. As in the staging of rectal cancer, where MRI is now a standard investigation, it has the potential to improve local staging as well as margin prediction in patients with oesophageal cancer being considered for surgery. Initial studies showed mixed results, with a sensitivity, specificity and accuracy for T

stage of 40%, 63% and 25-60% respectively and for N stage 25-58%, 67-88% and 56-72% respectively [95-97]. However, a subsequent study showed the accuracy of MRI to be much improved (81% for T stage and 63% for N status) [98]. Nodal staging may be significantly improved by the use of short inversion time inversion-recovery turbo spin-echo (STIR TSE) MRI with sensitivity, specificity, PPV and NPV of 81%, 98%, 93% and 95%, respectively in one study [99].

1.3 Neo-Adjuvant Oncological treatment

1.3.1 Neo-adjuvant chemotherapy - rationale for systemic therapy

The rationale for systemic therapy in adenocarcinoma of the oesophagus lies in the natural history of the disease, where most patients present with evidence of nodal or systemic metastases. Even those patients offered “curative” surgery die predominantly of metastatic disease, presumably due to the presence of occult micro-metastases at the time of surgery [32, 100]. Studies evaluating this phenomenon have demonstrated tumour cells in the bone marrow of patients undergoing resection in 40-65% of cases [101-103]. Even in patients deemed to be N0, further pathological analysis may demonstrate lymph node micro-metastases in 30% of patients [104, 105]. This presumably explains the poor results in historical series of surgically treated patients prior to the adoption of neo-adjuvant chemotherapy (NAC).

The perceived benefits of systemic chemotherapy include down-staging of the primary tumour [106] and the elimination of micro-metastases [107], supported by a number of studies showing reduced local and systemic recurrence [108-110]. However, a significant proportion of patients do not respond to NAC, and some develop progressive disease whilst on neo-adjuvant treatment. These latter tumours have poor biology and it is doubtful they were ever curable by surgery. Indeed, one might argue that these patients have avoided major futile surgery by undergoing chemotherapy which allows a time period for unfavourable tumours to declare themselves. In contrast, patients responding well to chemotherapy have a good long term prognosis.

Three large randomised trials have shown a survival benefit for NAC in oesophageal cancer [109-111]. The largest trial (OEO-2) randomised 802 patients to 2 cycles of

Cisplatin and 5 Fluorouracil (CF) followed by surgery or surgery alone, demonstrating significantly improved R0 resection rates in the NAC group (60 vs 54% p<0.0001) and improved overall survival (5year survival 23% vs 17% p=0.03) [111, 112]. A further UK based trial (MAGIC) predominantly recruited patients with gastric cancer, however 26% of patients with junctional tumours were also included and randomised to peri-operative chemotherapy (epirubicin, cisplatin and 5 fluorouracil - ECF) and surgery or surgery alone [109]. It demonstrated a significant survival benefit for chemotherapy (5 year survival 36% vs 23% p=0.009). A randomised trial from France (FFCD) recruited 224 patients to peri-operative CF and surgery or surgery alone, demonstrating an improved 5 year overall survival (38% vs 24% p=0.02) and disease free survival (DFS) (p=0.003) with chemotherapy [110]. In contrast to MAGIC, this latter trial was comprised of predominantly lower oesophageal and OGJ tumours (75%), however the benefits of chemotherapy in terms of survival and recurrence rates were strikingly similar. Notably, in both trials, completion of adjuvant chemotherapy was poor, with only 50-65% of patients commencing chemotherapy following surgery and even fewer (42-50%) completing it.

Whether peri-operative chemotherapy offers improved outcomes compared to a solely neo-adjuvant strategy remains contentious. Although OEO-2 demonstrated a survival benefit for NAC, this conflicted with the results of two other trials (RTOG 8911 and EORTC 40954) both of which failed to show any survival advantage for neo-adjuvant chemotherapy, despite improved surgical resection rates [113, 114]. Meta-analyses, subsequently confirmed an overall survival benefit for NAC [115, 116]. Interestingly, the benefit for chemotherapy appeared to be driven by the AC sub-group (HR 0.78 CI 0.64-0.95 p=0.014) rather than SCC sub-group (HR 0.88 CI 0.75-1.03 p=0.12)[117]. Complete pathological response may be found in 2.5 – 13% of patients following NAC and these patients have excellent 5 year survival [109].

In the UK, chemotherapy practice has evolved to reflect the results of these trials. NAC with CF was widely adopted following the successful completion of OEO-2, and this was expanded to 6 cycles of the peri-operative ECF regimen with the publication of the MAGIC trial. Subsequently, the demonstration that 5FU could be successfully replaced by the oral fluoro-pyramidine capecitabine in a RCT, led to ECX (epirubicin, cisplatin and capecitabine) largely replacing ECF [118]. Whether this additional neo-adjuvant chemotherapy translates into a survival benefit is currently being investigated in a further RCT, comparing 2 cycles of CF with 4 cycles of ECX (OEO-5 **NCT00041262**).

1.3.2 Neo-adjuvant chemo-radiotherapy

The rationale for neo-adjuvant chemo-radiotherapy (NACRT) is based on the sensitivity of oesophageal tumours to radiation and the principle of radio-sensitization, whereby chemotherapy augments the effects of radiotherapy leading to synergistic DNA damage and inhibition of cell repair [119]. A number of trials have demonstrated a survival benefit following NACRT [3, 120] and although they were not without significant flaws, this practice was widely adopted in in North America, Australasia and parts of continental Europe. Most notable was the study by Walsh and colleagues which demonstrated a significant survival advantage for NACRT and surgery over surgery alone (3 year survival 32% vs 6%) although this study was heavily criticised for the very poor survival in the surgery alone group and the inadequacy of staging [3]. A further randomised trial recruited 56 patients with AC or SCC to NACRT followed by surgery or surgery alone [120]. Despite closing early, due to poor accrual, the authors reported a survival benefit for NACRT (5 year survival 39% vs 16%). However, an Australasian trial randomised patients with AC and SCC to NACRT and surgery or surgery alone (62% AC 38% SCC) showing no difference in OS or DFS. Sub-group analysis suggested that patients with SCC had better DFS than AC with this approach (HR 0.47 vs 1.02) [121]. A number of other trials have failed to show any benefit for NACRT [122-125]. However, a subsequent meta-analysis supported the use of CRT as did a review of meta-analyses [117, 126].

The publication of the CROSS trial, which randomised 366 patients (75% AC; 23% SCC) to NACRT and surgery or surgery alone, demonstrated a survival advantage for NACRT (OS 49 vs 24 months p=0.003) [127]. The overall benefit was strongly driven by the improved survival in the SCC sub-group (p=0.007), whilst the adjusted HR for AC did not reach statistical significance (p=0.07). CPR rates were 30%, again favouring SCC patients (CPR 49% SCC vs 23% AC) and complete surgical resection rates reached an impressive 93%. Anastomotic leak rates were 22% and 30% in the tri-

modality and surgery alone groups respectively, raising questions as to the adequacy of surgery. The authors concluded that NACRT should be the standard of care for oesophageal cancer. However, the amalgamation of AC and SCC patients as well as the presence of a surgery alone control arm, remain overt weaknesses of this influential study.

The impact of this trial on UK practice remains to be seen. Certainly, the current philosophy of treating resectable lower oesophageal SCC with NAC followed by surgery has been challenged by the results of CROSS, which convincingly suggests that these patients may benefit most from tri-modality therapy.

However, the argument for AC is less convincing owing to the reduced sensitivity of these tumours to radiotherapy (XRT), the higher rates of systemic metastases in AC patients (compared to SCC which is more loco-regional [22]) and the much less convincing results from the CROSS trial in the AC sub-group.

One criticism of NACRT regimens is the compromise in systemic chemotherapy delivery that such treatment entails. Certain chemotherapy drugs, such as epirubicin, are contraindicated with concurrent XRT and others require a dose reduction. Attempts to maintain chemotherapy doses with XRT, as adopted in the Walsh trial (CF), resulted in a regimen with high levels of toxicity. The significantly lower radio-sensitising doses of chemotherapy employed in the CROSS trial are considered inadequate by proponents of chemotherapy, who argue that the logic for a reduction in systemic therapy is fundamentally flawed, given that adenocarcinoma is predominantly a systemic disease. They stress that this regimen is only suitable for localised radio-

sensitive tumours, such as those found in the SCC sub-group, which unsurprisingly skewed the overall survival benefit seen in the CROSS trial.

Study	Platinum	Fluoropyrimidine	Other
CROSS	Carboplatin AUC2 x 5		Paclitaxel 50mg/m2 x 5
MAGIC total	Cisplatin 360mg/m2	5FU 25200mg/m2	Epirubicin 300mg/m2
MAGIC neoadjuvant	Cisplatin 180mg/m2	5FU 12600mg/m2	Epirubicin 150mg/m2
FFCD total	Cisplatin 600mg/m2	5FU 18200mg /m2	
FFCD neoadjuvant	Cisplatin 300mg/m2	5FU 9600mg/m2	

Fig. 4 *Summary of systemic chemotherapy delivery in major trials. The equivalent Carboplatin dose to that employed in the MAGIC trial (Cisplatin 60mg x 3) is AUC4 and for FFCD (Cisplatin 100mg x 3) it is AUC 5/6. In MAGIC, the Cisplatin dose was reduced to accommodate the additional Epirubicin. A three weekly "systemic" Paclitaxel dose is 200mg. For comparison, the equivalent total chemotherapy dose would therefore be Carboplatin AUC 4 plus Paclitaxel 200mg x 6 plus Epirubicin (MAGIC)or Carboplatin AUC 5/6 plus Paclitaxel 200mg x 6 (FFCD)both of which represent much higher doses of chemotherapy than the radio-sensitizing AUC 2 plus Paclitaxel 50mg x 5(CROSS). Reproduced with permission EC Smythe*

Despite high CPR rates of 30% following NACRT, the majority (78%) of patients suffering a recurrence following this treatment, do so with systemic metastases. This pattern may be independent of the degree of response seen in the primary tumour on pathological analysis [128]. In a cohort study specifically assessing outcomes in patients with a CPR after NACRT, 5 year survival was only 50% with over 75% of the recurrences being systemic [129]. The authors highlighted a local recurrence rate of 13% as justification for the pursuit of local control with XRT, however the inadequacy of systemic therapy in a group of patients with no residual primary tumour was arguably the most important finding of this study. The principle that measures to improve local control do not necessarily translate into a survival advantage was also demonstrated in the MUNICON II trial [130]. In this prospective study, PET was used to identify non-

responders to NAC, with these patients being diverted to CRT prior to surgery. This led to an improvement in pathological tumour regression, but interestingly no reduction in R1 resection rates and no OS benefit because of high rates of systemic recurrence [130].

1.3.3 Studies comparing NAC to NACRT

A number of studies have attempted to compare NAC and NACRT with conflicting results [131-133]. An important distinction should be made between the different NACRT regimens which vary in their delivery of chemotherapy. Some use concurrent chemotherapy and XRT with a radio-sensitizing dose of chemotherapy (CROSS), whilst others use sequential induction chemotherapy followed by CRT, with the greater total exposure to chemotherapy that this entails. Stahl et al adopted this latter philosophy and randomised 126 patients with AC from 19 centres to NAC/surgery or induction chemotherapy/CRT/surgery [131]. Although this study was underpowered, 3 year survival showed a non-significant trend towards improved survival in the tri-modality group (3 year survival 47 vs 27% p=0.07). Notably, this group had significantly fewer patients with N0 disease, a difference which could not be explained by local down-staging as tumour regression scores were similar between the groups. As these patients were not matched for clinical nodal status before randomisation, this raised the possibility that the CRT group had earlier stage disease from the outset. Although only patients under 70 years of age with a WHO classification of 0 or 1 were considered for this trial, in hospital mortality was high following CRT (10.2% vs 3.8% p=0.26), some might argue unacceptably so. Other criticisms of this trial included the low accrual, the merger of oesophagectomy and gastrectomy patients and the high number of centres required to recruit a small volume of patients.

A further Australasian trial recruited 75 patients to receive neo-adjuvant chemotherapy or chemoradiotherapy prior to surgery [132]. Both regimens utilised similar doses of chemotherapy. Despite higher rates of pathological response following NACRT (major response 8% vs 31% p=0.01) 5 year survival was similar (36% vs 45% p=0.60), leading the authors to acknowledge the high rates of systemic disease that determined most patients' outcomes.

A single institution comparison of NAC versus NACRT showed no overall or disease-free survival difference, and no reduction in local recurrence following CRT, despite higher rates of CPR (17% vs 4%) in this group. The authors noted higher complication rates (48% vs 33%, p=0.09) and mortality (6% vs 0% p=0.12) following NACRT [133].

In a large meta-analysis, 24 studies were analysed incorporating 4188 oesophageal cancer patients [134]. These trials consisted of NAC vs surgery alone (9 trials; 1981 patients), NACRT vs surgery alone (12 trials; 1854 patients) and NAC vs NACRT (2 trials; 194 patients and 1 cohort study; 159 patients). Notably, the results of the MAGIC trial were excluded from analysis as it was not possible to differentiate those patients treated for junctional (oesophageal) cancers as opposed to gastric cancers. The HR for all-cause mortality, using surgery alone controls, was 0.87 for NAC (95% CI 0.79 – 0.96 ; p=0.005) and 0.78 for NACRT (95% CI 0.70 – 0.88; p<0.0001). Both adenocarcinomas and squamous cell carcinomas were included in this overall analysis. Interestingly, the overall significance for NAC was driven predominantly by the AC sub-group (HR AC 0.83; 95% CI 0.71 – 0.95 ; p=0.01), compared to the NACRT group which was driven by the improvements observed in the SCC sub-group (HR SCC 0.80; 95% CI 0.68 – 0.93 ; p=0.004).

In an attempt to compare NAC and NACRT, the authors pooled the data from the 2 small trials that specifically examined this hypothesis (both described above and neither showing statistically significant results) with the remainder of the trials from the meta-analysis (none of which directly compared the two strategies). However, unlike the main results which distinguished AC and SCC, the pooled data did not adjust for these sub-groups. Hence, although the HR comparing NAC and NACRT (HR 0.88; 95% CI 0.76 – 1.01; p=0.07) is often quoted by proponents of NACRT to favour this approach, its applicability to AC patients is questionable at best. The significant

heterogeneity of neo-adjuvant chemotherapy regimens in both arms was a significant confounder that could not be adjusted for within the remit of this study.

A further consideration in deciding the optimal neo-adjuvant treatment strategy is the morbidity and mortality created by the addition of XRT to chemotherapy. In a fragile, nutritionally deplete group of patients, NACRT may be poorly tolerated, with the quoted mortality of this treatment alone averaging 3% (range 0-15%), higher than the post-operative mortality reported in many surgical series. Those progressing to surgery may have higher rates of respiratory complications, anastomotic dehiscence, fistulation [123, 135-137] and even death [138-140].

Table 1 Summary of selected trials for operable esophagogastric cancer

Trial	Year	Disease type	Stage	*N*	Treatment	Survival	% of patients with local relapse only (%)	% of patients with regional/distant relapse (%)
Pre-operative chemotherapy								
RTOG 8911 [15, 35]	2007	Adenocarcinoma 53 % SCC 47 % Esophageal/GEJ 100 %	Not stated T4 tumours were excluded	467	Surgery Preoperative chemotherapy (3 cycles of cisplatin + 5-FU)	26 % 23 % (3 years OS) HR not reported	21 % 19 % (patients with R0 resections only)	51 % 49 % (patients with R0 resections only)
EORTC 40954 [13]	2010	Adenocarcinoma 100 % Proximal gastric 53 % Middle gastric 26 % Distal gastric 21 %	≥T3 98 % ≥N1 91 %	144	Surgery Preoperative chemotherapy (2 cycles of cisplatin + 5-FU)	70 % 73 % (2 year OS) HR 0.84, 95 % CI 0.52–1.35, p = 0.466	NR NR	NR NR
OEO2 [14]	2009	Adenocarcinoma 66.5 % SCC 30.8 % Middle/upper 1/3 25 % Lower 1/3 and Cardia 75 %	Not stated	802	Surgery Neoadjuvant chemotherapy (2 cycles of CF)	17.1 % 23.0 % (5 years OS) HR 0.84, 95 % CI 0.72–0.98, p = 0.03	12.2 11.5	19.4 24.2
Perioperative chemotherapy								
MAGIC [10]	2006	Adenocarcinoma 100 % Gastric 74 % Lower esophageal/GEJ 26 %	≥T3 63 %[b] ≥N1 73 %	503	Surgery Perioperative chemotherapy (3 cycles of preoperative ECF and 3 cycles of postoperative ECF)	23.0 % 36.3 % (5 years OS) HR 0.75, 95 % CI 0.6–0.93, *P* = 0.009	20.6 14.4	36.8 24.4
FNCLCC-FFCD [12]	2011	Adenocarcinoma 100 % Lower esophagus 11 % GEJ 64 % Stomach 25 %	≥T3 68 %[b] ≥N1 80 %	224	Surgery Perioperative chemotherapy (2–3 cycles of pre-op CF and 3–4 cycles of postop CF)	24 % 38 % (5 year OS) HR 0.69, 95 % CI 0.5–0.95, *P* = 0.02	8 12	38 30
Adjuvant chemotherapy								
ACTS-GC [11, 18]	2007	Adenocarcinoma 100 % Gastric 100 %	Stage ≤II 51 % Stage ≥III 49 % ≥T3 45 %	1059	Surgery Adjuvant chemotherapy (1 year of S-1)	61.1 % 71.7 % (5 year OS) HR 0.669, 95 % CI 0.540–0.828	3.2[a] 2.1	42.5[a] 31.8
CLASSIC [8, 19]	2012	Adenocarcinoma 100 % GEJ 2 % Gastric 98 %	≥T3 45 % ≥N1 90 %	1035	Surgery Adjuvant chemotherapy (8 cycles of XELOX)	69 % 78 % (5 years OS), *P* = 0.0029	8.5 4.0	15.1 9.4

Fig. 5 *Summary of trials using NAC or NACRT [141]. (Reproduced with permission Springer Japan 2014)*

Table 1 continued

Trial	Year	Disease type	Stage	*N*	Treatment	Survival	% of patients with local relapse only (%)	% of patients with regional/distant relapse (%)
Pre-operative chemoradiotherapy								
Stahl et al. [24]	2009	Adenocarcinoma 100 % GEJ 100 %	≥T3 100 %	126	Neoadjuvant chemotherapy (2.5 cycles of PLF) Neoadjuvant chemoradiotherapy (2 cycles of PLF then 3 weeks of CRT)	27.7 % 47.4 % (3 years OS) HR 0.67, 96 % CI 0.41–1.07, $P = 0.07$	23.7 15.0	22.0 16.7
Tepper et al. [25]	2009	Adenocarcinoma 75 % SCC 25 % Distal esophagus/GEJ 100 %	≥N1 25 %	56	Surgery Neoadjuvant chemoradiotherapy (50.4 Gy + cisplatin + 5-FU)	1.79y 4.48y (median OS) HR not reported $p = 0.002$	16 16	41.6 37.5
CROSS [26, 28]	2012	Adenocarcinoma 74 % SCC 23 % Upper 1/3, middle 1/3 16 %, distal 1/3 57 % GEJ 24 %	≥T3 81 % ≥N1 64 %	366	Surgery Neoadjuvant chemoradiotherapy (carboplatin + paclitaxel + 41.4 Gy)	44 % 58 % (3 years OS) HR 0.657, 95 % CI 0.495–0.871, $P = 0.003$	9.3 %[c] 3.3 %[c]	47.8 %[c] 31.5 %[c]
Post-operative chemoradiotherapy								
INT-0116 [20]	2001	Adenocarcinoma 100 % Gastric 80 % Cardia 20 %	≥T3 68 % ≥N1 85 %	556	Surgery Adjuvant chemoradiotherapy (45 Gy + 5-FU)	41 % 50 % (3 year OS) HR 1.32, 95 % CI 1.1–1.6, $P = 0.0046$	8.0 2.0	57.0 38.0
ARTIST [21]	2012	Adenocarcinoma 100 % GEJ 5 % Gastric 95 %	≥T3 NR ≥N1 86 % Stage ≤II 59 % Stage ≥III 41 %	458	Adjuvant Chemotherapy (6 cycles of XP) Adjuvant Chemoradiotherapy (2 cycles of XP followed by 46 Gy XRT and 2 cycles of XP)	74.2 % 78.2 % (3 year DFS) HR not reported $p = 0.0862$	8.3 4.8	24.6 20.4

CF cisplatin and 5-fluorouracil, *DFS* disease-free survival, *ECF* epirubicin, cisplatin and 5-fluorouracil, *GEJ* gastroesophageal junction, *NR* not reported, *OS* overall survival, *PLF* cisplatin, fluorouracil, leucovorin (each cycle lasted 6 weeks), *SCC* squamous cell carcinoma, *XELOX* capecitabine and oxaliplatin, *XP* capecitabine and cisplatin, *XRT* radiotherapy with concomitant capecitabine

[a] Some patients had first relapse at more than one site. Including lymph nodes. [b] Varies according to treatment arm; this is the surgery alone arm. [c] Includes 54 patients from the phase II CROSS trial

1.3.4 Biological therapies

The over-expression of numerous receptors in oesophageal cancer has led to a therapeutic interest in the targeting of these receptors with biological agents. A number of trials have investigated the use of Bevacizumab (an Antibody against VEGF) in unresectable AC [142, 143] showing improved survival. The idea that VEGF expression may be increased by NAC makes it a particularly attractive target in this setting. Trastuzamab (an Antibody to HER-2) has been combined with Cisplatin and Paclitaxel in advanced AC, with an OS of 24 months, supporting a role for HER-2 inhibition in these patients [144].

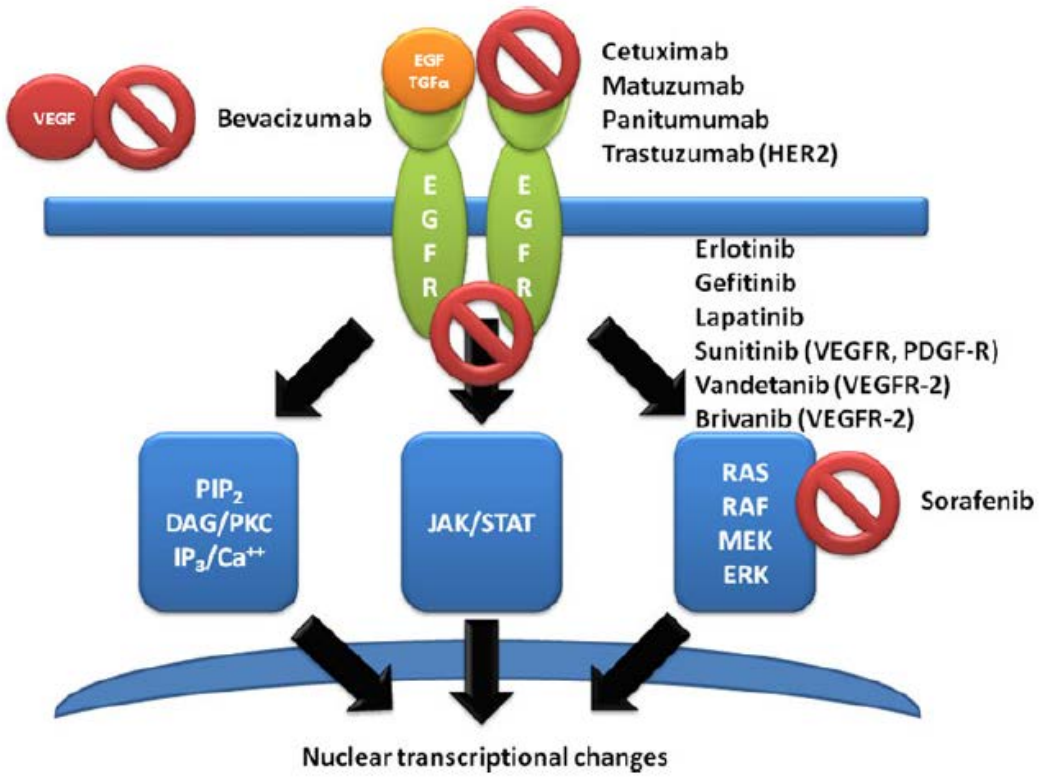

Fig. 6 *The EGF receptor family is a group of receptor tyrosine kinases that result in activation of the JAK/STAT, RAS/RAF, and PKC pathways. Bevacizumab is a VEGF inhibitor. Cetuximab, matuzumab, and panitumumab inhibit the EGF receptor at the ligand-binding site, while trastuzumab inhibits the HER-2 receptor via the same mechanism. Erlotinib, gefitinb, and lapatinib inhibit the tyrosine kinase moiety for the EGF receptor, while vandetanib and brivanib have the same mechanism of inhibition for the VEGFR-2 receptor. Sunitinib inhibits the tyrosine kinase moiety for the VEGF and PDGF receptors. Sorafenib is a selective RAF kinase inhibitor [145]. (Reproduced with permission Springer science & business media)*

The TOGA trial, although focussed on advanced gastric cancer, also showed a benefit for Trastuzamab in combination with CF both in terms of OS (13.5 vs 11 months p=0.005) and PFS [146]. The RTOG0436 trial (**NCT 00655876**) amongst others has investigated the monoclonal Antibody Cetuximab (EGFR) in combination with CRT [147, 148].

1.3.5 On-going and future trials

The results of a number of on-going randomised trials will further inform decision-making. The OEO-5 trial has compared 2 cycles of neo-adjuvant CF to 4 cycles of ECF, with the intention of defining the role of additional neo-adjuvant chemotherapy in oesophageal cancer. The STO-3 trial **(NCT00450203)** recruited over 1000 patients, randomising to peri-operative chemotherapy with or without Bevacizumab in operable oesophago-gastric adenocarcinoma. This trial, which finished accrual in 2013, also included a feasibility study assessing lapatinib (EGFR Tyrosine Kinase Inhibitor) in HER-2 positive cancers.

The MAGIC vs CROSS Trial **(NCT01726452)** is an on-going RCT that aims to compare NAC, according to the MAGIC trial regimen, and NACRT using the CROSS regimen to identify which groups, if any, may benefit from trimodality therapy.

The CRITICS trial **(NCT00407186)** was designed to assess the role of adjuvant chemo-radiation in the context of modern systemic therapy regimens. It compares peri-operative ECX (3 cycles before and after surgery) to neo-adjuvant ECX (3 cycles), followed by adjuvant CRT.

The TOXAG study **(NCT01748773)** is assessing the role of trastuzamab in addition to CRT in the adjuvant setting for HER 2 positive gastric and OGJ tumours. A further trial based in the USA **(NCT01196390)** is adding Trastuzamab to neo-adjuvant CRT (paclitaxel and carboplatin).

The CALGB group **(NCT 01333033)** have initiated a study aiming to recruit 200 patients with OGJ tumours to undergo NAC followed by a PET scan performed after cycle 3. Non responders on PET (<35% reduction in SUV) will cross over to concurrent CRT with the primary intention of achieving a CPR in 20% of these “non-responding” patients. The stated secondary outcome measure for this group is overall survival.

1.4 Re-staging after chemotherapy

With the widespread adoption of neo-adjuvant chemotherapy for oesophageal cancer in the UK, many studies have attempted to assess the accuracy of staging modalities at predicting response to such treatment. Tumour assessment following neo-adjuvant therapy may be considered as two different entities, the first being TNM re-staging to provide an anatomical tumour stage following chemotherapy. The second is an estimation of response to NAC that aims to predict pathological tumour regression. Traditionally, the latter has provided a qualitative assessment of the tumour with questionable decision-making value. More recently, attempts at quantifying such response have led to a more standardised objective approach, incorporating anatomical and physiological parameters.

Endoscopy and re-biopsy have a sensitivity of 60% and 36%, specificity of 34% and 100%, PPV of 49% and 100% and NPV of 44% and 24% respectively in predicting pathological response after CRT [149].

Staging after chemotherapy remains challenging as most modalities, particularly CT and EUS, struggle to differentiate viable tumour from fibrosis. The presence of an oesophageal stent can also make this staging assessment particularly unreliable. Historically, CT assessment has been poor at re-staging tumours following NAC and NACRT. Various methods of quantifying tumour response on CT have been proposed, the commonest being the RECIST (Response evaluation criteria in solid tumours) criteria where tumour size is used to categorize tumours into complete response, partial response, stable disease or progressive disease [150, 151]. CT volume assessment

has also been used, with volume change correlating with pathological response in some studies [152] but not others [153].

A comprehensive literature review compared CT with EUS and PET in the assessment of tumour response to chemotherapy showing CT accuracy (54%) to be inferior to both EUS (86%; p=0.003) and PET (85%; p=0.006) [72]. Other studies have confirmed CT to be less accurate than EUS and PET for both early and late assessment of response to NAC [71].

EUS may have the ability to predict pathological response but published studies have been inconsistent with the quoted sensitivity, specificity and accuracy ranging from 50-100%, 36-100% and 67-100% respectively [154]. In a meta-analysis of EUS, the accuracy of re-staging for T stage and N status was 58% and 62% respectively [72, 154]. A number of single institution series have concluded that EUS is of limited benefit in the re-staging of oesophageal cancer, mainly due to difficulties in assessing T stage and identifying complete responders to NAC [155]. However, most showed EUS to perform better at nodal re-staging and response assessment. A prospective study of 41 patients compared cross-sectional area changes on EUS following CRT, to Mandard TRG [156]. Twenty out of 23 (87%) pathological responders had evidence of an endoscopic response and 10/13 (77%) non-responders on definitive pathology had no endoscopic response (PPV 80%; NPV 81%).

The addition of FNA to EUS may improve the reassessment of N stage, reaching 78% in one study [157]. Others have successfully utilised EUS and FNA to identify residual nodal disease after NACRT (sensitivity 82%, accuracy 68%), despite concerns over false positive results caused by traversing the primary tumour to reach the target lymph

node [158, 159]. Given the importance of nodal disease on overall prognosis, and particularly persistent nodal disease following chemotherapy, this represents an interesting finding.

It may be concluded, on the basis of currently available evidence, that EUS struggles to identify T stage after NAC, but may be useful in N staging and overall response assessment, both of which are arguably more important from a prognostic perspective [154]. Despite this, EUS is not commonly performed after NAC in the UK.

PET has been widely studied in the prediction of response to neo-adjuvant chemotherapy. Numerous PET parameters have been used to assess response to therapy including standardised uptake variable (SUV), mean tumour volume (MTV), total lesion glycolysis (TLG) and tumour heterogeneity. In a review of the literature, most studies showed that a reduction in SUV following NAC predicted pathological response [160-164]. In some studies this physiological response on PET also translated into a survival benefit. In a meta-analysis of 13 studies, the pooled sensitivity of PET for response assessment after NAC was 70.3% with a specificity of 70.1% [165]. A subsequent study showed even better sensitivity, specificity and accuracy of PET response prediction reaching 86,93 and 90% respectively [160].

PET response may be assessed early following commencement of chemotherapy (e.g. after the first or second cycle of treatment) or may be delayed until after the completion of neo-adjuvant therapy [166]. It has been proposed that early and late PET imaging may examine slightly different facets of response [167]. The former has the theoretical advantage of providing an earlier insight into the response of the tumour to chemotherapy, potentially expediting a change in strategy in the absence of a

response. Delayed PET may assess residual tumour following completion of therapy [167, 168]. In a review of the literature, early PET assessment (reduction in SUV) after cycle 1 of chemotherapy predicted response in all six studies, whereas delayed PET did so in only 2 out of 6 studies. The authors concluded that early PET response assessment was preferable to delayed imaging [164].

Prospective studies, including the MUNICON trial, have shown that a reduction in SUV at 14 days following commencement of NAC predicts pathological response and survival [160, 169, 170]. In this study, the authors used a PET based algorithm to divert patients to early surgery in the absence of a response to chemotherapy [170].

One of the criticisms of the many studies evaluating PET response to chemotherapy has been the significant heterogeneity encountered in the patient groups. For example, the inclusion of adenocarcinomas and squamous cell carcinomas, the use of different NAC regimens and even the use of XRT in sub-groups makes data interpretation difficult. PET may be more unreliable following NACRT due to the profound inflammatory reaction created by this treatment [171]. Other studies have lacked consensus in terms of their definition of pathological response and the cut-offs used to define PET response. Some have proposed a 35% reduction in SUV as distinguishing responders from non-responders [170]. Further studies suggested a 50% reduction in SUV after NAC predicted DFS, down-staging (sensitivity 78%, specificity 53%, PPV 57%, NPV 75%) and pathological response (sensitivity 90%, specificity 45%, PPV 24%, NPV 96%) [172]. Other studies have contradicted this finding entirely, showing no relationship between PET parameters and survival, recurrence or pathological response [173]. The lack of consistency in the literature was highlighted by a systematic review on PET response which did not proceed to meta-analysis due to significant heterogeneity in the dataset [174].

As a result, alternative parameters measurable by PET imaging have also been assessed. Tumour volume change after CRT, calculated according to a 40% threshold from maximum SUV, correlated with pathological response whereas other parameters including SUV did not [175]. PET heterogeneity may also predict response better than SUV and with new markers emerging all the time, this is a rapidly evolving field. Even allowing for study variations, the consensus remains that PET/CT provides the best available evaluation of tumour response to NAC and it is therefore surprising that this has not been adopted as standard in the UK [157].

Multi-parametric MRI has the potential to improve chemotherapy response assessment, although published studies are generally small. Compared to CT, it can provide a multi-functional assessment of the tumour and superior soft tissue characterisation, without exposure to radiation.

Dynamic contrast-enhanced MRI (DCE-MRI) uses the flow of gadolinium contrast between blood vessels and the extra-cellular space to quantify tumour perfusion and permeability [176]. Following NAC, tumour vasculature may return to normal such that the porosity of blood vessels decreases, thus reducing the extravasation of contrast into the extracellular space [177]. Radiation may induce the opposite effect due to the release of pro-angiogenic factors [178, 179].

Blood oxygenation level dependent (BOLD) MRI measures tumour oxygenation using the differing magnetic characteristics of oxygenated and de-oxygenated haemoglobin (Hb) [180]. Tumour oxygenation may increase in patients who are responding to NAC due to improved vascularisation and tumour perfusion [181].

Diffusion weighted (DW) MRI assesses the diffusion of water molecules within a given tissue. Cellular structures may restrict diffusion and the ability to measure this phenomenon provides a surrogate for cellularity. Apparent diffusion coefficient (ADC) is a measureable parameter that reflects and quantifies this principle. Hence areas of high cellularity have a low ADC and vice versa [182]. It has been hypothesised that ADC should increase in those patients who are responding well to NAC as a result of treatment induced cell death.

A prospective study investigated the ability of diffusion weighted MRI to predict pathological response following the neo-adjuvant treatment of OGJ tumours [183]. This study recruited 32 patients, predominantly with AC (81%), who had been treated with NAC or NACRT. Mandard TRG was used to quantify pathological response. Pre- and post-treatment DW-MRI scans were used to compare ADC and tumour volumes. Tumour volume parameters were unable to predict pathological response. However, a low initial ADC value and a significant increase in ADC during chemotherapy predicted pathological responders with sensitivity, specificity, PPV, NPV, accuracy and AUC of 88%, 87%, 88%, 87%, 88% and 0.909, respectively. Thus, the authors concluded that ADC may have a role in predicting pathological response in oesophageal cancer.

A further study compared DW-MRI and PET/CT in early response assessment following NAC [184]. 15 patients with OGJ tumours underwent both imaging modalities on the same day, before and after treatment. High levels of concordance (73%) were found between changes in ADC and SUV. Absolute ADC values were also significantly different between pathological responders and non-responders (p=0.043).

Taken together, these studies justify the further evaluation of MRI in oesophageal cancer staging. It has shown promise in local tumour staging, margin prediction, the assessment of nodal status and the prediction of response to neo-adjuvant treatment, although it remains to be seen whether it improves decision making over and above currently available staging modalities. However, it may be that MRI can provide, in one staging assessment, the equivalent information to that currently available from multiple investigations and may therefore have the potential to simplify staging algorithms.

Imaging heterogeneity is a technique which quantifies the intensity and distribution of pixels within a given image [185]. Entropy and uniformity are the baseline parameters that comprise heterogeneity, with preliminary evidence suggesting a prognostic role in oesophageal cancer [186-188]. In a retrospective study of 31 patients who received NAC, change in heterogeneity predicted survival (36 months vs. 11 months, $p<0.001$) [186]. A further study showed a significant correlation between CT heterogeneity parameters and PET SUV in 21 oesophageal cancer patients [188]. Another study evaluated the role of PET heterogeneity in 41 patients who underwent definitive CRT [92]. PET heterogeneity (sensitivity 76-88%, specificity 73-91%) appeared to predict treatment response more accurately than SUV (sensitivity 53-71%, specificity 45-73%). Hence heterogeneity, measured on both CT and PET based imaging, may predict survival and could be used as an adjunctive tool in treatment response assessment.

With on-going developments in imaging technology, the optimal re-staging algorithm has yet to be fully defined. A significant challenge is how to implement multiple staging investigations, within an already complex pathway, without over-burdening the patient with tests. A further consideration is how to improve staging accuracy whilst at the same time adhering to the recommended guidelines for initiation of treatment that exist

in the UK. This time constraint already puts significant pressure on the patient pathway and is not conducive to a significant increase in the number of staging investigations.

1.5 Treatment of oesophageal cancer

1.5.1 Surgery

The role of radical surgery in oesophageal cancer is controversial, as it has been in the treatment of many other tumour types. In part this is due to the different philosophies of treating cancer, one of which mandates a radical operation to remove the tumour with wide margins, including all regional lymph nodes, with “curative” intent. The more pragmatic approach is to regard surgery to remove the primary tumour as one component of a multi-modality strategy, on the basis that oesophageal cancer often represents a systemic disease at presentation. As such, tumour response to systemic therapy primarily dictates the prognosis in all but the earliest tumours.

Historically, radical surgery was widely adopted in the management of breast cancer, resulting in mutilating operations for questionable benefit. The advent of targeted systemic and hormonal therapies as well as the long terms results of trials have demonstrated this radical approach to be of little benefit. As a result, breast conserving surgery as opposed to mastectomy is now offered to most women with breast cancer and sentinel node sampling has largely replaced axillary clearance in the management of regional lymph nodes [189-191]. Both of these policies are supported by extensive scientific evidence in favour of a less radical approach. Indeed, more recent data suggest that patients with confirmed metastatic disease in a sentinel node may not benefit from axillary surgery at all, on the basis that local recurrence is rare and may not be reduced by axillary clearance anyway [192].

Oesophageal cancer due to its propensity for metastatic dissemination has a worse outlook than breast cancer and it is therefore logical that the majority of patients will require systemic therapy. Surgery in isolation is seldom indicated, a principle supported by historical series which have rarely demonstrated 5 year survival to exceed 20% with this approach [123, 193, 194]. Current guidelines recommend that only T1 tumours should be managed by primary surgery and even a proportion of these patients may be suitable for endoscopic resection [195]. Given that peri-operative systemic therapy is recognised as a standard of care for most patients with oesophageal cancer, it is surprising that contemporaneous randomised trials have continued to include surgery alone control arms [127].

Transhiatal oesophagectomy (THO) involves abdominal and cervical incisions, with abdominal and lower mediastinal lymphadenectomy performed under direct vision and an anastomosis sited in the neck. Its proponents argue that the avoidance of a thoracotomy reduces the rate of post-operative complications, and that an anastomotic leak in the neck has significantly less morbidity and mortality than a leak in the mediastinum [4, 196, 197]. Transthoracic oesophagectomy (TTO) involves a 2-stage procedure, incorporating abdominal and thoracic components which facilitate dissection of the tumour under direct vision and a more extensive mediastinal lymphadenectomy. Access may be achieved via the right or left chest, the former being the most common.

Extended lymphadenectomy undoubtedly improves staging accuracy [198] but whether it improves loco-regional disease control or overall survival remains contentious. The most influential study to examine the number of lymph nodes required to adequately classify N status concluded that 12 lymph nodes resulted in a 90% sensitivity [199]. A further study concluded that 15 lymph nodes were required to provide sufficient staging

information and that this translated into a survival advantage [200]. Based on worldwide data, a further study proposed criteria for an adequate lymphadenectomy based on tumour T stage (**T1** : 10 lymph nodes, **T2** : 20 lymph nodes, **T3/4** : 30 lymph nodes) [201]. However this recommendation far exceeds the average US experience of lymphadenectomy, reported as 13 lymph nodes by the American College of surgeons study group [202].

How much of the perceived benefit of radical surgery is due to the focus on achieving an R0 resection, as opposed to radical lymphadenectomy is also the subject of much debate [203]. Either way, the choice of incisions should not be confused with radicality, as the presence of a thoracotomy per se does not guarantee a “radical” approach to the primary tumour has been performed [204]. Standardisation of surgical technique has undermined many studies that have attempted to address the role of surgical radicality in oesophageal and gastric cancer [205].

Most studies analysing more versus less radical oesophageal cancer surgery have failed to demonstrate any survival benefit for a more radical approach. The principal RCT to address this question showed higher rates of morbidity following radical surgery (TTO) with no benefit in terms of overall survival [206]. At five year follow-up, sub-group analysis, although underpowered, suggested that some groups may benefit from the more radical transthoracic approach, namely oesophageal (as opposed to junctional) tumours and those patients with a limited number of involved lymph nodes(1-8 nodes) [207]. Other randomised trials [208-210], meta-analyses [4, 211-213] and case series have demonstrated similar survival following transhiatal and transthoracic resection. The question of whether morbidity is increased by the addition of a thoracotomy is also somewhat contentious with a number of studies suggesting higher mortality and respiratory morbidity [4, 213, 214]. Other studies have contradicted this finding, and indeed

some complications such as recurrent laryngeal nerve (RLN) palsy and anastomotic stricture are more common after THO [212, 213].

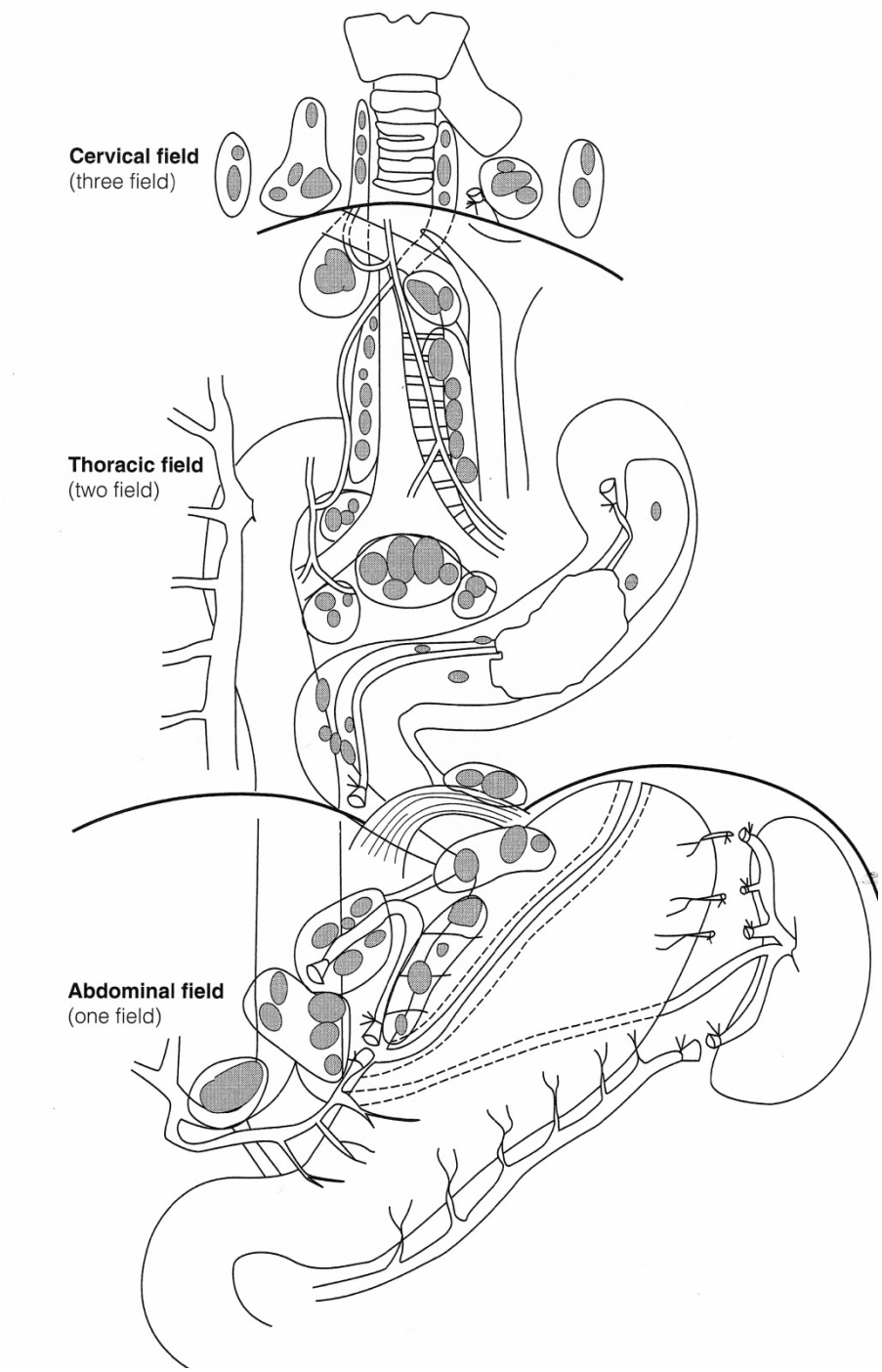

Fig. 7 *Lymphadenectomy fields in oesophageal cancer surgery. Published in Companion to specialist surgical practice – oesophago-gastric surgery 2013. SM Griffin. Reproduced with permission Elsevier 2014*

The principle of radical surgery has been extended further in Japan to include 3 field lymphadenectomy i.e. cervical node dissection in addition to the abdominal and mediastinal lymphadenectomy typically performed during transthoracic surgery. The rationale for extended resection was prompted by reportedly high rates of isolated tumour recurrence in the neck following transthoracic surgery for SCC [215]. In a small RCT of 62 patients, 2 field and 3 field lymphadenectomy were compared, showing no difference in survival or recurrence but a higher rate of complications in the 3 field group [216]. The authors emphasised a trend towards survival improvement with the 3 field approach as justification for adopting this approach. However, the data from Japan almost exclusively consists of patients with SCC, making any application to western patients difficult to interpret. As a result, 3 field lymphadenectomy for western patients with adenocarcinoma has not been widely accepted and the 2 field Ivor-Lewis transthoracic approach remains the most common operation for oesophageal cancer surgery.

1.5.2 Minimally invasive oesophagectomy (MIO)

Whilst the short term mortality following oesophageal resection has fallen considerably in recent years, it remains an operation with high rates of morbidity and a significant impact on quality of life. This has inevitably heralded a search for minimally invasive approaches to the oesophagus and enhanced recovery programmes to minimise the surgical insult [217, 218]. MIO has been successfully adopted in high volume units, but remains a technically challenging procedure with a prolonged learning curve. In a report of over 1000 MIO procedures performed in a single unit, in-hospital mortality was 1.7% with a median hospital stay of 8 days and comparable oncological outcomes to open surgery [219]. Early reports of the successful implementation of MIO prompted a prospective, multi-institution study showing low rates of mortality (<2%) and an overall survival of 50% at 3 years [220]. Numerous other studies have compared open surgery to MIO [221-223]. In a recent systematic review of 1100 patients, MIO was associated with reduced blood loss, reduced morbidity and reduced hospital stay compared to open oesophagectomy [224].

1.5.3 Barrett's surveillance and Endoscopic mucosal resection for early cancer

With the recognition of the role of Barrett's oesophagus in the development of oesophageal adenocarcinoma and the introduction of endoscopic surveillance programmes for such patients, there has emerged a cohort of patients with HGD and intra-mucosal adenocarcinoma in whom a therapeutic dilemma exists. Whilst surgery offers excellent long term survival for these patients, the morbidity and mortality associated with oesophagectomy might be considered excessive, given the low probability of lymph node metastases in early tumours [225, 226]. This has led to the search for viable alternatives such as endoscopic mucosal resection (EMR) and endoscopic sub-mucosal dissection (ESD). Based on the assumption that early disease (≤ T1a) can be accurately identified by currently available staging modalities, EMR allows for resection of early tumours with low morbidity and mortality [226]. Whilst long term results are awaited, the undoubted advantages in a correctly selected group of patients make this an appealing alternative to surgery.

1.5.4 Definitive Chemo-radiotherapy

Alternatives to surgical resection for oesophageal cancer are appealing for obvious reasons. Herskovic (RTOG 85-01) published the seminal study analysing definitive CRT vs XRT alone demonstrating significantly improved OS and DFS in the CRT arm, albeit with high rates of local recurrence (47%) [227]. Other studies have reported encouraging survival results following definitive CRT, rivalling those for surgery, stage for stage [228, 229]. Elderly patients, particularly those with SCCs treated by CRT, had improved outcomes compared to best supportive treatment in one study, and comparable survival to surgery in another, strengthening the argument for non-operative management in this sub-group of patients [228, 230]. In a further trial assessing the role of high dose versus low dose radiotherapy in SCC (INT 0123) no benefit was seen with increased radiation [231]. Indeed, for most patients with SCC, primary CRT with salvage surgery for those patients with residual or recurrent cancer, appears to be the direction of travel [232].

1.5.5 Adjuvant treatment

The evidence for adjuvant therapy is less convincing for oesophageal cancer as indeed it has been for other tumours such as rectal cancer. In principle, it does not share some of the perceived advantages of neo-adjuvant treatment, namely the guaranteed early delivery of systemic therapy with the potential to down-stage the primary tumour and improve surgical resection margin rates. In rectal cancer, only patients who responded to neo-adjuvant treatment gained any benefit from adjuvant chemotherapy in one study [233]. Whilst this may be intuitive, little evidence currently exists to guide adjuvant therapy in oesophageal cancer.

In the US, the Macdonald study (INT 0116) [234] demonstrated a benefit for adjuvant CRT (36 months vs 27 months $p<0.01$), although 80% of patients recruited had gastric cancer and only 10% of patients had a D2 resection. Therefore, the criticism levelled at this trial was that CRT compensated for inadequate surgery. Trials assessing adjuvant chemotherapy (as opposed to neo-adjuvant or peri-operative treatment) have largely failed to show an overall survival advantage for this approach [235, 236]. However, the relative improvement in survival seen with peri-operative chemotherapy (MAGIC, FFCD) compared to a solely neo-adjuvant strategy (OEO-2) is taken by some, as indirect evidence of a benefit for adjuvant treatment.

The impact of peri-operative chemotherapy may be considerable, with toxicities related to the treatment and on-going nutritional deficiencies providing multi-disciplinary challenges. The fact that over 50% of patients recommended for adjuvant chemotherapy in the aforementioned randomised trials did not complete their treatment, emphasises the enormous cumulative physical insult of multi-modality therapy. The addition of XRT almost certainly adds to this overall morbidity. Whether patients with minimal response to chemotherapy on pathological analysis should be

offered adjuvant treatment, and the role of changing chemotherapeutic agents in this context, remains unknown.

1.5.6 Quality of life after oesophageal cancer surgery

The recovery from oesophageal cancer surgery is prolonged and extends far beyond the date of discharge from hospital. Numerous quality of life studies have concluded that the resolution of physical symptoms and restoration of emotional well-being may take up to three years following surgery [237, 238]. Some functions will never return to baseline. Post-operative complications are known to adversely affect QOL and survival [239]. With the benefit of hindsight, any patient not surviving long enough to regain their pre-operative QOL, would have been better served by alternative oncological therapies to surgery [240]. This “break-even” point for patients undergoing surgery may vary, but appears to be 12-18 months from the date of operation.

1.5.7 Recurrence after oesophageal cancer surgery

The likelihood of recurrence after oesophageal cancer surgery is predominantly determined by the stage of the tumour at the time of resection. Loco-regional recurrence may occur in the tumour bed, regional lymphatics or at the anastomotic site, the latter often precipitated by an involved margin at the time of surgery. Distant metastatic recurrence most frequently occurs in the liver and lungs although numerous other sites have been described. Although termed “recurrence”, these metastases were most likely present, albeit undetectable, at the time of surgery.

The timing of recurrence tends to be mainly within the first 2 years from surgery, and is a devastating outcome for a patient still recovering from extensive treatment. Distant metastases tend to present earlier than loco-regional recurrences, possibly related to poor tumour biology or, alternatively, the insidious onset of local symptoms from the mediastinum [241]. Adenocarcinomas have a greater tendency to metastasise systemically than SCCs, which have a more loco-regional pattern of dissemination, frequently affecting the mediastinal and cervical lymph nodes [23, 24, 198, 242].

Historically, routine surveillance imaging for the detection of recurrence has not been indicated due to the lack of available second line treatment options. However, the increasing recognition of biological markers and the availability of targeted therapies for tumours expressing these markers may justify a change in approach. That said, disease recurrence after surgery is seldom cured and in the absence of effective second line therapy, the emphasis of treatment is to manage symptoms and maintain quality of life.

2. Aims

One of the major challenges in oesophageal cancer management is the acquisition of high volume data which can provide a baseline for standards of care and the guidance of new management strategies. Whilst most advances in oncological therapies are guided by the results of multi-centre randomised trials, many research questions are not feasible to address in such trials. Therefore, the results of large institutional cohort series remain important as they reflect true working practice, and may address several research questions simultaneously.

The aim of this thesis was to consolidate and analyse a large prospectively collected database of oesophageal resections with a view to assessing :-

1. Factors associated with early recurrence and death after oesophageal cancer surgery
2. The role of surgical radicality in the management of oesophageal cancer
3. The down-staging effects of neo-adjuvant chemotherapy in oesophageal cancer

3. Methods

These studies utilised a database of 680 consecutive oesophageal resections performed over a ten year period (2000-2010). This involved a research collaboration between two high volume institutions (St Thomas' hospital and Royal Marsden hospital) based in London, United Kingdom. All surgeries were performed with curative intent for malignant or pre-malignant tumours of the oesophagus or oesophago-gastric junction (type 1 and 2 according to Siewert's classification). Tumours with an epicentre greater than 2cm distal to the true junction were regarded as Type 3 and thus excluded from analysis. Staging and management principles were very similar between the two units, and incorporated OGD, CT, EUS and latterly PET in the initial assessment of these tumours. Patients with OGJ tumours underwent additional laparoscopy. Patients deemed eligible for a radical treatment pathway were then considered for primary surgery or neo-adjuvant chemotherapy. Re-staging after NAC utilised CT (thorax, abdomen & pelvis) but not routinely EUS or PET. Surgery was performed or supervised by three surgeons. Surgical approach included transhiatal or transthoracic resection, the latter subdivided into left thoraco-abdominal or Ivor-Lewis resections, primarily dictated by surgeon preference. Pathological analysis was performed by one member of a dedicated team of histopathologists. Staging utilised the 7th edition of the TNM classification.

The database, initiated in 2000, was prospectively maintained and included all patients undergoing surgery for oesophageal cancer between 2000 and 2010. Data were rigorously cross-referenced with all available sources to ensure accuracy. These included prospective hospital databases, hospital records (notes and lab records), cancer registry and GP (General Practitioner) records to ensure long term outcome data were robust. Three major STH database reviews were conducted during this

period (2003, 2006 and 2010) whereby pathological and outcome data were checked and cross-referenced. Some additional fields were added to the database during this process with these fields requiring retrospective data supplementation. On each occasion the reviews were performed by two independent researchers. The RMH database was also independently verified in 2011 by a professional data collector. Missing data was pursued rigorously, driven by the prospective decision to exclude patients from multi-variable analysis if more than one data field was missing. Survival was updated in May 2012, according to the last confirmed attendance to a hospital or GP practice.

Recurrence was defined as radiological or histological evidence of disease as agreed by multi-disciplinary team consensus. This was further sub-divided into loco-regional (confined to the anastomosis, tumour bed or lymph nodes considered local to the original site of the primary tumour e.g. mediastinum or left gastric territories), distant (haematogenous, peritoneal or distant lymph node spread) or both.

Data analysis was performed with the assistance of an experienced bio-statistician from an aligned academic unit at Karolinska Institutet, Stockholm, Sweden and was independently verified. Prior to the commencement of each studies' statistical analysis a manual cross-checking process performed by two data managers ensured the database had not been corrupted. Analysis utilised SAS (version 9.2 SAS Institute Inc., Cary, NC, USA).

Ethical approval for use of the database was granted by the Integrated research application system (IRAS reference : 12-NW-0511).

From the outset, the intention was to submit this thesis by publication route. It therefore incorporates three manuscripts, each containing their own specific introduction, methods, results and conclusion sections. Each study used a separate prospective study protocol (Appendix) agreed by the authors before any statistical analyses were performed. Whilst some deviations from protocol were made at the request of journal editors, these represented only minor adaptations to the original protocols.

4. Early recurrence and death after oesophagectomy (study 1)

Factors associated with early recurrence and death after esophagectomy for cancer

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Factors Associated with Early Recurrence and Death After Esophagectomy for Cancer

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Background: Accurate selection of patients for radical treatment of esophageal cancer is essential to avoid early recurrence and death (ERD) after surgery. We sought to evaluate a large series of consecutive resections to assess factors that may be associated with this poor outcome.
Methods: This was a cohort study including 680 patients operated for esophageal cancer between 2000 and 2010. The poor outcome group comprised 100 patients with tumor recurrence and death within 1 year of surgery. The comparison group comprised 267 long-term survivors, defined as those surviving more than 3 years from surgery. Pathological characteristics associated with poor outcome were analyzed using logistic regression to determine odds ratios (OR) and 95% confidence intervals (CI).
Results: On the adjusted model T stage and N stage predicted poor survival, with the greatest risk being patients with locally advanced tumors and three or more involved lymph nodes (OR 10.6, 95% CI 2.8–40.0). Poor differentiation (OR 2.8, 95% CI 1.4–5.5), chemotherapy response (OR 3.6, 95% CI 1.2–10.6), and involved resection margins (OR 2.7, 95% CI 1.2–6.0) were all significant independent prognostic markers in the multivariable model. There was a trend toward worse survival with lymphovascular invasion (OR 2.0, 95% CI 0.9–4.2) and low albumin (OR 1.9, 95% CI 0.8–4.4) but not of statistical significance in the adjusted model.
Conclusions: Esophageal cancer patients with poorly differentiated tumors and three or more involved lymph nodes have a particularly high risk of ERD after surgery. Accurate risk stratification of patients may identify a group who would be better served by alternative oncological treatment strategies.
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Key Words: esophageal cancer; recurrence; surgery

INTRODUCTION

Early tumor recurrence and death within 1 year of esophagectomy for esophageal cancer must be considered a failure of accurate pre-operative staging and patient selection. Tumor recurrence is the leading cause of death in patients undergoing esophageal cancer resection, with the majority recurring within 1 year of surgery [1–3]. In order to justify an extensive therapeutic insult such as esophagectomy, there should be a reasonable prospect of improving duration of survival with acceptable quality of life.

Patients who do not survive a minimum of 1 year after surgery, rarely regain their pre-operative levels of activity or quality of life [4–7]. These patients, therefore, need to be identified before surgery as they would often be better treated by other therapies.

A number of factors are known to be associated with poor prognosis in esophageal cancer, but unfortunately many of these are only confirmed after resection of the specimen, limiting their practical use at the time of surgical decision-making [8]. Accurate prediction of chemotherapy response remains elusive, and there is not currently a reliable method of determining suitability for surgery.

The aim of this study was to assess clinicopathological factors associated with early recurrence and death (ERD) within 1 year of surgery for esophageal cancer. We evaluated a large series of consecutive resections, where the ERD group was compared to a group of long-term survivors (LTS). To our knowledge this is the first such study to specifically assess early esophageal cancer recurrence in western patients.

METHODS

Study Design

This was a cohort study based on two prospectively collected databases from St. Thomas' Hospital and Royal Marsden Hospital, both high-volume units for esophageal cancer surgery in London, United

Abbreviations: CI, confidence interval; CT, computed tomography; CPR, complete pathological response; CRP, C-reactive protein; ERD, early recurrence and death; EUS, endscopic ultrasound; FDG-PET, fluorodeoxyglucose positron emission tomography; GP, general practitioner; HGD, high grade dysplasia; LTS, long-term survival; MRI, magnetic resonance imaging; MDT, multi-disciplinary team; OR, odds ratio; RCP, Royal College of Pathologists, UK.

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Kingdom. Included in the source study cohort were 680 consecutive patients who underwent surgical resection of esophageal or esophagogastric junction (Type I or II) tumors with curative intent during the period 2000–2010 inclusive. The follow-up ended in March 2012.

The two comparison groups were those with tumor recurrence and mortality within 1 year of surgery (ERD) and those who survived at least 3 years from operation (LTS). Three years was chosen on the basis that few patients suffer from tumor recurrence after this period [9]. The minimum follow-up period was 12 months allowing every patient to be potentially eligible for the ERD group.

Clinical Management

Patients underwent a standard protocol of investigation, including esophago-gastro-duodenoscopy, computed tomography (CT), endoscopic ultrasound (EUS), and fluorodeoxyglucose positron emission tomography (FDG-PET). Chemotherapy practice evolved during the period of study, and followed standard indications and regimens supported by randomized trial data [10,11]. This meant that patients with T2 tumors (or greater) and/or node positive disease on initial staging were considered eligible for induction therapy. All patients were managed by a recognized upper gastrointestinal cancer multi-disciplinary team (MDT).

Surgical resections included transthoracic ($n = 412$) and transhiatal ($n = 268$) esophagectomies with choice of approach determined by individual surgeon preference.

Histological staging of the resected specimens was standardized to meet the updated 7th Edition TNM criteria to allow for comparison [12].

Follow-Up

At the time of updating the database, survival was recorded according to the last confirmed attendance to a hospital or general practitioner (GP) clinic. Tumor recurrence was assessed by way of histological or radiological confirmation of disease, as agreed by the MDT.

Statistical Analysis

Unconditional logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI). Crude and multivariable analysis was performed. The variables included in the multivariable model were: age (<56, 56–69, >69 years old), pathological tumor stage (T0-2 N0/1/2-3, T3-4 N0/1/2-3), tumor grade (moderately or poorly differentiated), response to chemotherapy (complete pathological response (CPR), good—moderate response and poor—no response, no chemotherapy and unknown response [patients had chemotherapy but Mandard score not documented]), margin status (R0, R1/2), lymphovascular invasion (positive/negative) and pre-operative albumin (<40, ≥40). Patients were excluded from the model if they had one or more missing variable ($n = 8$). The additional discrepancy in patient numbers between Tables I and II was accounted for by the perfect correlation of HGD, CPR, and well-differentiated tumors with LTS.

Our initial intention was to include albumin and C-reactive protein (CRP) in the main multivariable model but due to the lack of available data from the early study period this would have resulted in loss of statistical power. Sufficient numbers of patients had albumin data to be included in a smaller model that included all of the above parameters. CRP was not entered into multivariate analysis. All analyses were performed using SAS, version 9.2 (SAS Institute, Inc., Cary, NC).

RESULTS

Patients

Among all 680 patients in the source study cohort, the overall survival at 1 year was 80% with estimated survival (Kaplan–Meier) of 57% and 45% at 3 and 5 years, respectively. In-hospital mortality was 2%.

The ERD group comprised 100 patients who died within 12 months of surgery with proven recurrence, while the LTS group included 267 patients (Fig. 1).

The pattern of early recurrence in the ERD group was loco-regional (18%), distant metastases (57%) or both (25%), while in the LTS group, late recurrence was more likely to be loco-regional (40%), although metastatic (38%) and combined recurrences (22%) were still common.

Time to recurrence was shorter in patients with metastatic disease (5 months) than loco-regional relapse (6 months).

Characteristics

Age, sex, and histological sub-type were similar between the groups (Table I). The ERD group contained a higher frequency of more advanced tumors with a greater burden of nodal disease and higher grade of tumor differentiation. A greater proportion of patients underwent perioperative chemotherapy in the ERD group (ERD 84% vs. LTS 56%) reflecting their more advanced disease. More patients had incomplete resections in the ERD group (ERD R0 19% vs. LTS R0 74%) with almost all (96%) of these R1 resections due to involvement of the circumferential resection margin, defined as tumor at or within 1 mm of the radial margin. Lymphovascular invasion was more likely in the ERD group (ERD 70% vs. LTS 25%) as was a low pre-operative albumin (ERD 57% vs. LTS 43%) and raised pre-operative CRP (ERD 55% vs. LTS 31%). Length of post-operative hospital stay was similar between the groups (ERD 16 days vs. LTS 15 days). Post chemotherapy CT in the ERD group demonstrated progressive disease in 4 patients, stable disease in 36 patients, partial response in 40 patients and no visible disease in 4 patients. Sixteen patients did not undergo chemotherapy.

Risk of Early Recurrence and Death

Older age did not strongly influence the OR of ERD (Table II). Pathological tumor stage was strongly associated with ERD, with the greatest OR encountered in patients with locally advanced tumors (T3–T4) and in those with three or more involved lymph nodes (OR 10.6; 95% CI 2.8–40.0). Other adverse prognostic features included pathological tumor grade, where poor differentiation heralded an adjusted OR of 2.8 (95% CI 1.4–5.5) compared to moderately differentiated tumors.

Poor histological response to chemotherapy (adjusted OR 3.2; 95% CI 1.1–8.8) and positive margin status (adjusted OR 2.7; 95% CI 1.2–6.0) were independent predictors of ERD. The point OR estimates showed worse survival with lymphovascular invasion (adjusted OR 2.0; 95% CI 0.9–4.2) and pre-operative albumin (OR 1.9, 95% CI 0.8–4.4), but they were not statistically significant. To minimize the cohort heterogeneity, further analysis was performed excluding the patients with squamous cell carcinoma, but no impact on the overall results or independent prognostic features was found after such exclusion (data not shown).

DISCUSSION

This study indicates that pathological tumor stage, tumor grade, completeness of resection, and poor response to chemotherapy are independent indicators of ERD after esophageal cancer surgery, while albumin and lymphovascular invasion might also be predictors of such outcomes.

The novelty of the present study is mainly its design. We have specifically sought to identify those factors associated with a clearly defined outcome sufficiently poor, that it could guide decision-making, specifically the avoidance of surgery. This is the first study to assess this in a cohort of western patients with adenocarcinoma.

TABLE I. Demographics and Tumor Characteristics of the Study Patients Who Had Undergone Resection for Esophageal Cancer With Early Recurrence & Death or Long-Term Survival (Alive 3 Years After Surgery)

	Early recurrence and death		Long-term survivors	
	n	%	n	%
Number of patients	100	—	267	—
Age (mean (range))	62 (28–81)	—	62 (32–81)	—
Male: female	78:22	78:22	214:53	80:20
Adenocarcinoma: squamous	89:11	89:11	206:35	85:15
Chemotherapy (%)	84	84	150	56
Tumor stage				
T0-2 N0	5	5	127	48
T0-2 N1	5	5	34	13
T0-2 N2-3	10	10	15	5
T3-4 N0	9	9	51	19
T3-4 N1	15	15	21	8
T3-4 N2-3	56	56	19	7
Grade (differentiation)				
CPR	1	1	15	6
HGD	0	0	23	9
Well	0	0	16	6
Moderate	41	41	156	58
Poor	58	58	57	21
Chemotherapy response				
Complete	1	1	15	6
Good/moderate	9	9	60	22
Poor/no response	48	48	39	15
No chemotherapy	16	16	117	44
Unknown response	26	26	36	13
Margin status				
R0	19	19	195	74
R1/2	81	81	70	26
Lymphovascular invasion				
Negative	29	30	195	75
Positive	69	70	65	25
Albumin				
Normal ($\geq$40)	33	43	123	57
Abnormal ($<$40)	44	57	91	43
Hospital stay (median (range))	16 (7–191)	—	15 (7–127)	—

Some methodological issues deserve attention. The study allowed for the long-term follow-up of a large series of consecutive esophageal cancer resections. The comparison of a worst outcome group of patients with a good outcome group made the outcomes distinct. Moreover, the ability to adjust the results for relevant prognostic factors was an advantage. Finally, although the sample size of the cohort was large, the study did not have statistical power to verify weak or moderate associations.

A potential bias is the selection of cases to the two referral hospitals for esophageal cancer surgery. However, staging and management principles were similar and there were no major differences in post-operative mortality or stage-matched survival. The cohort's heterogeneity in terms of operative approach was countered by the fact that surgical strategy (transhiatal or transthoracic esophagectomy) did not have any impact on survival or recurrence (data not shown). Additionally, the principle of treating adenocarcinoma and squamous cell carcinoma as distinct pathological entities was adhered to by the confirmation that our results were unchanged by the exclusion of squamous carcinomas on subsequent analysis.

A large study from China assessed early recurrence after resection for squamous cell carcinomas of the esophagus, concluding similar markers of adverse prognosis to those found in our study [1]. Approximately 52% of the recurrences in their series were metastatic disease with the remainder being local or regional.

Our series almost exclusively focused on adenocarcinoma and 82% of patients recurring and dying within 12 months of surgery had metastatic disease. The timing and pattern of disease recurrence is of interest as it provides an insight into the mechanism of failure. Our study clearly suggests that the most significant obstacles to good patient selection for surgery are the identification of occult metastases and how to measure response to treatment by accurately re-staging patients after chemotherapy. CT appears unable to discriminate patients with a very poor outcome after surgery as evidenced by the fact that nearly half of the patients in the ERD group had some evidence of tumor regression on their post-chemotherapy scan. This would suggest that alternative re-staging modalities such as PET-CT should be further assessed after chemotherapy with the ability to assess physiological response to treatment. This modality has the added benefit of improved sensitivity for the detection of occult metastases.

Of particular interest is to identify high-risk patients based on the information that could realistically be available at the time of surgical decision-making. Improved loco-regional staging is essential given the clear importance of T stage and N stage on the overall prognosis. T stage can be predicted with an accuracy of greater than 80% on EUS [13,14], but this test is less useful in predicting tumor downstaging after chemotherapy due to its inability to differentiate tumor from fibrosis [15,16]. Potential advances may be brought about by future improvements in CT, EUS, and magnetic resonance imaging (MRI). The latter may also have a role in predicting circumferential resection margin involvement [17,18].

Nodal status, and particularly patients with multiple ($\geq$3) lymph nodes involved do particularly poorly but, despite its importance, it

TABLE II. Odds Ratios (OR) and 95% Confidence Intervals (CI) of Early Recurrence and Death After Esophagectomy for Esophageal Cancer

	Crude		Adjusted*	
	OR	95% CI	OR	95% CI
Age (years)				
<56	1 (Ref)	–	1 (Ref)	—
56–69	0.9	0.5–1.7	0.9	0.4–2.0
>69	1	0.5–2.0	1.3	0.5–3.3
Tumor stage				
T0-2 N0	1 (Ref)	—	1 (Ref)	—
T0-2 N1	3	0.8–12.1	2.4	0.6–10.4
T0-2 N2-3	13	3.6–46.9	5.2	1.2–22.0
T3-4 N0	3.7	1.1–12.8	1.6	0.4–6.1
T3-4 N1	15.2	4.5–51.5	4.6	1.1–18.9
T3-4 N2-3	58.5	18.7–182.3	10.6	2.8–40.0
Grade (differentiation)				
Moderate	1 (Ref)	—	1 (Ref)	—
Poor	3.8	2.3–6.3	2.8	1.4–5.5
Chemotherapy response				
Good/moderate	1 (Ref)	—	1 (Ref)	—
Poor/no response	7.8	3.4–17.7	3.2	1.1–8.8
No chemotherapy	1.1	0.5–2.8	0.9	0.3–2.6
Unknown response	5.2	2.2–12.7	3.6	1.2–10.6
Margin status				
R0	1 (Ref)	—	1 (Ref)	—
R1/2	9.8	5.4–17.6	2.7	1.2–6.0
Albumin				
≥40	1 (Ref)	—	1 (Ref)	—
<40	1.8	1.0–3.2	1.9	0.8–4.4
Lymphovascular invasion				
Negative	1 (Ref)	—	1 (Ref)	—
Positive	5.7	3.4–9.7	2	0.9–4.2

*Adjusted for age, tumor stage, grade, chemotherapy response, margin status, albumin, and lymphovascular invasion.
1 (Ref) = reference value.

remains extremely difficult to assess this accurately after neo-adjuvant treatment. The addition of EUS with fine needle biopsies after chemotherapy may have a further role to play in this respect although this is not currently standard practice in our unit [19]. One study has demonstrated EUS to have an accuracy of 68% and sensitivity of 82% at determining nodal status after neo-adjuvant chemoradiotherapy [20]. A recent study has successfully utilized PET-CT in the accurate evaluation of nodal status after chemotherapy for squamous cell carcinoma and this may well add discriminatory power to decision making prior to surgery [21].

Poor differentiation on pathological tumor grading independently tripled the likelihood of ERD compared to patients with moderately differentiated tumors. Tumor grade can be predicted pre-operatively from endoscopic biopsies, and confirmed poor differentiation cannot be ignored as an ominous prognostic sign.

Chemotherapy response is perhaps the most important component of patient selection. FDG-PET has been widely championed as having a role in response prediction, and even selecting patients for salvage surgery in the absence of a response [22–25]. However, this has recently been challenged by a prospective study which failed to correlate FDG-PET results after chemoradiotherapy with pathological response, survival or recurrence [26]. It is therefore still unclear, whether anatomical (re-staging CT/EUS) or physiological (FDG-PET) assessment of tumor response is superior and whether indeed they correlate with definitive response seen at pathological examination.

Albumin and CRP are of particular interest as they can be easily measured pre-operatively. Although our data have not been able to fully assess these parameters, the latter not being included in multivariable analysis, there does seem to be an association with poor prognosis. Indeed, a number of studies have shown acute phase proteins to be prognostic and as such they merit assessment in further studies [27,28].

Circumferential margin status is prognostically important but this may be affected by the criteria used to define a positive margin [29,30]. Almost all (96%) of our R1 resections were related to CRM involvement, which at 38% overall, is in line with other published series after neo-adjuvant chemotherapy using the RCP definition [31]. This, in itself, identifies an area for potential improvement and inevitably, proponents of neo-adjuvant chemoradiotherapy would argue that this strategy may improve pathological response rates and reduce margin involvement, albeit with greater potential morbidity [32–34].

It is tempting to select patients at risk of margin involvement for escalation of neo-adjuvant therapy, whilst sparing those patients who may not benefit the extra morbidity of radiation. We have developed a predictive score for CRM involvement (data not shown) based on CT characteristics that shows encouraging results (specificity 98%, positive predictive value 86%) and could therefore be used in the context of our multivariable model to predict poor outcome and/or select patients for additional radiotherapy. It must also be remembered that the vast majority of patients dying within a year of surgery, are doing so with established metastatic disease suggesting that local control is not the predominant issue in the worst outlook patients. As such, any neo-adjuvant regimen must strive to maintain maximal systemic efficacy and compromising this in the pursuit of local control may have an adverse effect by lacking equivalent efficacy for occult micrometastases.

In our series, the combination of a locally advanced (T3/4) poorly differentiated adenocarcinoma, with three or more lymph nodes involved, a low pre-operative albumin and involved resection margin

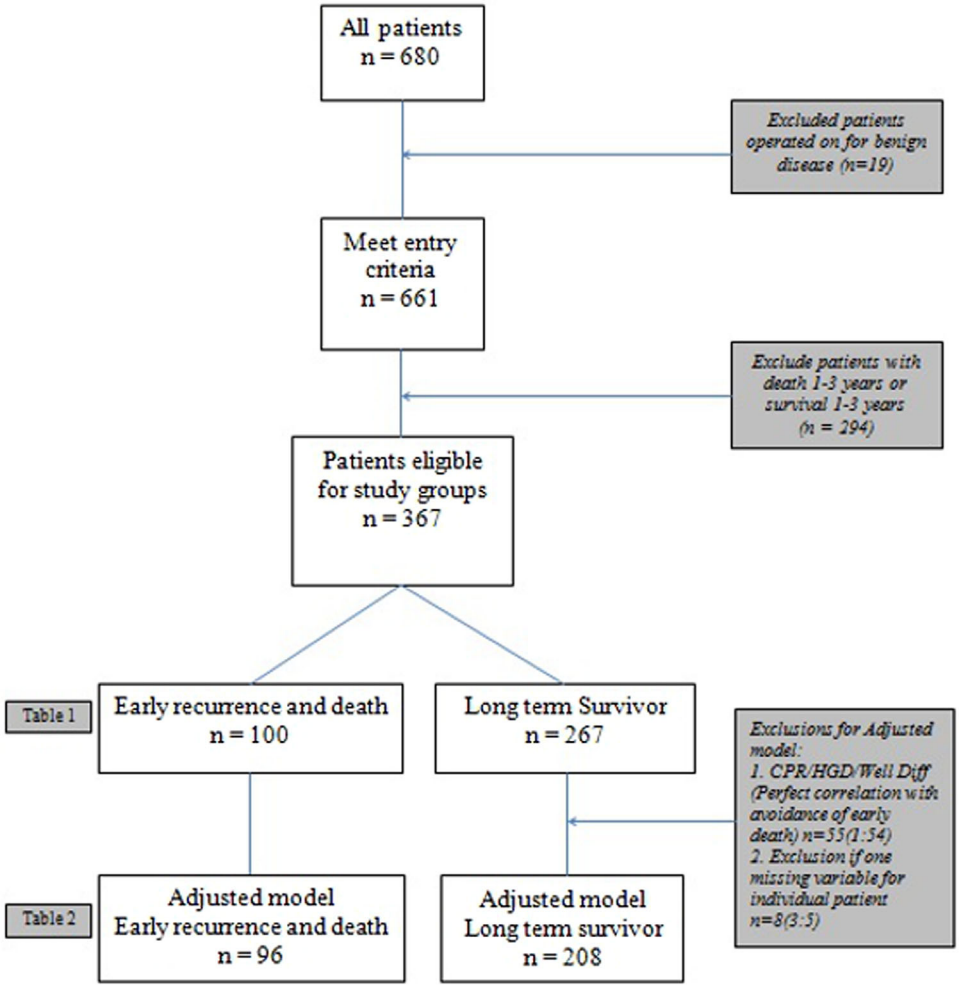

Fig. 1. Flow diagram summarizing patient allocation and exclusions.

resulted in a 75% risk of dying within 1 year and 85% risk within 18 months (almost all with recurrent cancer). This must be weighed against a 6% chance of surviving 3 years from surgery, with no significant survival difference between patients with N2 and N3 disease in this sub-group of patients. Whether this outcome is sufficiently poor to change practice is debatable but it may at least guide decision-making. In the absence of a clear response to treatment, it is difficult to justify surgery in this group of patients and perhaps the majority would be better served by alternative treatment strategies.

Despite this, it remains difficult to advise a patient with a technically resectable tumor not to have surgery on the basis of a predicted outcome. Molecular and biological markers may simplify this decision in the future [35,36]. In the meantime, we can only attempt to individualize therapy based on certain tumor characteristics, previous experience and patient wishes. Given the high proportion of patients developing early recurrence with metastatic disease, there needs to be renewed focus on the pre-therapeutic identification of occult metastases.

In conclusion, this study has highlighted the importance of advanced T stage (T3/4), N status (N2/3), and poor differentiation as markers of early poor outcome. A rigorous multi-disciplinary staging process should be capable of predicting these parameters with reasonable accuracy. The additional use of acute phase proteins and models to predict margin involvement may further risk stratify a group of patients in whom careful consideration must be given before embarking on surgery. Although assessment of response to chemotherapy continues to pose significant challenges, there can at least be some optimism that a robust prognostic scoring system with the ability to guide management strategy is achievable.

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5. Surgical radicality (study 2)

Surgical resection strategy and the influence of radicality on outcomes in oesophageal cancer

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Original article

Surgical resection strategy and the influence of radicality on outcomes in oesophageal cancer

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Background: The optimal surgical approach to tumours of the oesophagus and oesophagogastric junction remains controversial. The principal randomized trial comparing transhiatal (THO) and transthoracic (TTO) oesophagectomy showed no survival difference, but suggested that some subgroups of patients may benefit from the more extended lymphadenectomy typically conducted with TTO.

Methods: This was a cohort study based on two prospectively created databases. Short- and long-term outcomes for patients undergoing THO and TTO were compared. The primary outcome measure was overall survival, with secondary outcomes including time to recurrence and patterns of disease relapse. A Cox proportional hazards model provided hazard ratios (HRs) and 95 per cent confidence intervals (c.i.), with adjustments for age, tumour stage, tumour grade, response to chemotherapy and lymphovascular invasion.

Results: Of 664 included patients (263 THO, 401 TTO), the distributions of age, sex and histological subtype were similar between the groups. In-hospital mortality (1·1 *versus* 3·2 per cent for THO and TTO respectively; $P = 0{\cdot}110$) and in-hospital stay (14 *versus* 17 days respectively; $P < 0{\cdot}001$) favoured THO. In the adjusted model, there was no difference in overall survival (HR 1·07, 95 per cent c.i. 0·84 to 1·36) or time to tumour recurrence (HR 0·99, 0·76 to 1·29) between the two operations. Local tumour recurrence patterns were similar (22·8 *versus* 24·4 per cent for THO and TTO respectively). No subgroup could be identified of patients who had benefited from more radical surgery on the basis of tumour location or stage.

Conclusion: There was no difference in survival or tumour recurrence for TTO and THO.

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Introduction

The optimal surgical approach to tumours of the oesophagus and oesophagogastric junction is controversial. The debate centres principally on the philosophical principles underlying the treatment of oesophageal cancer, one of which mandates radical surgery with a level of lymphadenectomy that maximizes locoregional control and prevents the stepwise progression of disease. By definition, this requires transthoracic oesophagectomy (TTO).

A more pragmatic approach is to regard all but the earliest oesophageal cancers as a systemic disease at presentation, in which case the prognosis is determined predominantly by tumour biology. As such, surgery tailored mainly to removal of the primary tumour is an adjunct to the systemic therapy that will primarily dictate outcome. In this context, transhiatal oesophagectomy (THO) should not result in a survival disadvantage. Prediction of which patients may benefit from more extended surgery remains unclear from the literature.

The principal randomized clinical trial[1] to address this issue did not show any overall survival advantage with more radical surgery. Subgroup analysis[2], although underpowered, did suggest a benefit in some patients with a particular level of lymph node involvement at the 5-year follow-up.

The present analysis involved a large cohort of consecutive patients undergoing oesophageal resection in whom the surgical approach, THO or TTO, was dictated by surgeon preference, in order to assess the role of radicality in oesophageal cancer surgery. It was

hypothesized that more radical surgery (TTO) would provide an oncological survival benefit, on the basis of more complete mediastinal lymphadenectomy, and that extended dissection of perioesophageal tissue would reduce the rate of margin involvement (R1 resection).

Methods

This was a cohort study based on two prospectively created databases from St Thomas' Hospital and Royal Marsden Hospital, London, UK, involving consecutive patients who underwent surgical resection of oesophageal or oesophagogastric junction (Siewert type I or II[3]) tumours with curative intent between 2000 and 2010. Follow-up ended in July 2012. The primary outcome measure was overall survival following the surgical approach of THO or TTO. Secondary outcomes were time to tumour recurrence and the pattern of such recurrence.

Study patients underwent a standard protocol of investigation, including oesophagogastroduodenoscopy, computed tomography of the thorax, abdomen and pelvis, endoscopic ultrasonography and, since 2007, fluorodeoxyglucose positron emission tomography. Chemotherapy practice evolved during the period of study, and followed standard regimens supported by randomized clinical trial data[4,5]. Indications for chemotherapy were no different according to the unit of presentation or type of surgical resection planned. All patients were managed by a recognized upper gastrointestinal cancer multidisciplinary team.

TTO comprised right-sided transthoracic with separate abdominal phase (Ivor Lewis) and left thoracoabdominal approaches. Some of the Ivor Lewis resections utilized a laparoscopic abdominal phase. THO was performed via roof-top and cervical incisions, and included transhiatal dissection of the lower mediastinum under direct vision. The operative approach was determined by individual surgeon preference, with one surgeon performing either transhiatal or left thoracoabdominal resections and two surgeons performing Ivor Lewis resections exclusively.

Specimens were examined by dedicated upper gastrointestinal histopathologists in each unit. Histological staging of the resected specimens was standardized to meet the updated seventh edition of the tumour node metastasis (TNM) criteria[6] to allow for comparison.

Hospital mortality was defined as any postoperative death occurring before discharge from hospital. Patients entered a follow-up protocol that included 3-monthly clinic visits for the first year with surveillance computed tomography performed 3 and 6 months after surgery. Subsequently patients were reviewed every 6 months for 5 years, with further imaging based on clinical features.

At the time of updating the database, survival was recorded according to the last confirmed attendance to any hospital clinic, or, if discharged from surgical follow-up, the date last seen by their general practitioner. Tumour recurrence was assessed by histological or radiological confirmation of disease, as agreed by the multidisciplinary team.

Statistical analysis

Cox proportional hazards models were used to calculate hazard ratios (HRs) with 95 per cent confidence intervals (c.i.) for TTO compared with THO in relation to time to death or time to tumour recurrence. Both times were measured as continuous variables from the date of surgery. THO was used as the reference category. Survival was calculated by the Kaplan–Meier method.

Three models were used: a crude (unadjusted) model (model 1); a main model that adjusted for age (continuous), pathological tumour stage (categorized as T0 N0, T1–2 N0, T1–2 N1–3, T3–4 N0, T3–4 N1 or T3–4 N2–3), tumour grade (well, moderately or poorly differentiated), response to chemotherapy (complete pathological response, good or moderate response, and poor or no response representing Mandard tumour regression scores of 1, 2–3 and 4–5 respectively[7], no chemotherapy and unknown response (patient had chemotherapy but Mandard score not documented)), and lymphovascular invasion (positive or negative) (model 2); and an additional model that further adjusted for margin status (R0 or R1/2) and lymph node yield (less than 10, 10–19, 20–29, or 30 or more nodes) (model 3). These two additional prognostic markers in model 3 were excluded from model 2 because they were considered to represent a mechanism by which radical surgery might provide a survival advantage.

A positive circumferential resection margin (CRM) was defined as tumour at or within 1 mm of the radial margin according to Royal College of Pathologists criteria[8]. Lymph node yield was stratified according to previously validated Worldwide Oesophageal Cancer Collaboration (WECC) criteria[9] (required lymph node yield: T1 tumour, 10 or more nodes; T2, 20 or more nodes; T3–4, 30 or more nodes).

To evaluate the proportional hazards assumption, the correlation between Schoenfeld residuals[10], calculated as the difference between observed and expected covariable values for each patient who died, and failure time were tested. A non-significant relationship between these residuals and failure time supports the proportional hazards assumption. Stratified analyses were performed one by

one for tumour location (oesophageal, oesophagogastric junction types 1 and 2), T category ('early', T1–2; 'advanced', T3–4) and N category (N0, N1, N2 and N3) to see whether any association between surgical approach and outcome was modified by particular tumour characteristics.

All data management and analyses were performed using SAS® version 9.2 software (SAS Institute, Cary, North Carolina, USA). Data were analysed independently by an experienced biostatistician at a separate academic institution (Karolinska Institute, Stockholm, Sweden). $P < 0{\cdot}050$ was considered statistically significant.

Results

The source cohort consisted of 680 patients, of whom 15 patients who did not have surgery for malignant or premalignant disease, and one patient in the TTO group who died during surgery before tumour resection were excluded. Among the 664 patients included in the study cohort, 263 (39·6 per cent) underwent THO and 401 (60·4 per cent) had TTO. TTO comprised Ivor Lewis (325 patients) and left thoracoabdominal (76) approaches. The distributions for age, sex and histological subtype were similar between the groups, although there was a tendency towards more advanced tumour stage in the TTO group (*Table 1*). A lower proportion of patients in the THO group received neoadjuvant chemotherapy (47·1 per cent *versus* 78·1 per cent in the TTO group).

Postoperative outcomes

There were three in-hospital deaths (1·1 per cent) after THO and 13 (3·2 per cent) after TTO ($P = 0{\cdot}110$). Median (range) hospital stay was significantly shorter after THO (14 (7–95) *versus* 17 (8–191) days; $P < 0{\cdot}001$). In total, 108 patients (41·1 per cent) in the THO group developed tumour recurrence: locoregional in 32 patients (12·2 per cent), metastatic in 48 (18·3 per cent), and both locoregional and metastatic in 28 (10·6 per cent). This compared to 179 patients (44·6 per cent) with recurrence in the TTO group: locoregional disease in 40 patients (10·0 per cent), metastatic in 81 (20·2 per cent), and both locoregional and metastatic in 58 (14·5 per cent).

Overall survival was 80·2, 55·1 and 44·4 per cent at 1, 3 and 5 years respectively. Crude analysis indicated a survival benefit for THO, but in the adjusted model there was no difference in overall survival between the groups (HR 1·07, 95 per cent c.i. 0·84 to 1·36) (*Table 2*). Similarly, there was no difference in time to tumour recurrence in the adjusted model (HR 0·99, 0·76 to 1·29); however, when additional adjustments were made for margin status and

Table 1 Demographics and tumour characteristics according to surgical approach in patients with oesophageal cancer who underwent oesophagectomy

	THO group ($n = 263$)	TTO group ($n = 401$)
Age (years)*	64(10) (29–83)	64(10) (34–84)
Sex ratio (M : F)	217 : 46	317 : 84
Histology		
Adenocarcinoma	205 (77·9)	324 (80·8)
Squamous carcinoma	32 (12·2)	48 (12·0)
HGD	21 (8·0)	7 (1·7)
CPR	5 (1·9)	22 (5·5)
Tumour stage		
T0 N0	26 (9·9)	29 (7·2)
T1–2 N0	70 (26·6)	91 (22·7)
T1–2 N1–3	62 (23·6)	57 (14·2)
T3–4 N0	35 (13·3)	64 (16·0)
T3–4 N1	30 (11·4)	46 (11·5)
T3–4 N2–3	40 (15·2)	114 (28·4)
Tumour grade		
CPR, HGD, well differentiated	36 (13·7)	52 (13·0)
Moderately differentiated	143 (54·4)	217 (54·1)
Poorly differentiated	84 (31·9)	132 (32·9)
Chemotherapy response		
Complete	5 (1·9)	22 (5·5)
Good or moderate	51 (19·4)	89 (22·2)
Poor or no response	57 (21·7)	160 (39·9)
Unknown response	11 (4·2)	42 (10·5)
No chemotherapy	139 (52·9)	88 (21·9)
Lymphovascular invasion		
No	147 (55·9)	234 (58·4)
Yes	116 (44·1)	167 (41·6)
Margin status		
R0	155 (58·9)	240 (59·9)
R1	106 (40·3)	158 (39·4)
R2	2 (0·8)	3 (0·7)
Lymph node yield		
< 10	78 (29·7)	57 (14·2)
10–19	139 (52·9)	136 (33·9)
20–29	35 (13·3)	110 (27·4)
≥ 30	11 (4·2)	98 (24·4)
Death during follow-up		
No	129 (49·0)	179 (44·6)
Yes	134 (51·0)	222 (55·4)
Recurrence during follow-up		
No	155 (58·9)	222 (55·4)
Yes	108 (41·1)	179 (44·6)
Locoregional	32 (12·2)	40 (10·0)
Metastatic	48 (18·3)	81 (20·2)
Both	28 (10·6)	58 (14·5)
In-hospital mortality		
No	260 (98·9)	388 (96·8)
Yes	3 (1·1)	13 (3·2)
Hospital stay (days)†	14 (11–20) (7–95)	17 (13–26) (8–191)

Values in parentheses are percentages unless indicated otherwise; values are *mean(s.d.) (range) and †median (i.q.r.) (range). THO, transhiatal oesophagectomy; TTO, transthoracic oesophagectomy; HGD, high-grade dysplasia; CPR, complete pathological response; T, tumour; N, node.

Table 2 Multivariable analysis of time to death and tumour recurrence following transhiatal (reference) and transthoracic oesophagectomy for oesophageal cancer

	n	Hazard ratio	
		Time to death	Time to recurrence
Model 1			
All patients	664	1·35 (1·09, 1·68)	1·30 (1·02, 1·65)
Model 2			
All patients	664	1·07 (0·84, 1·36)	0·99 (0·76, 1·29)
Adenocarcinoma alone	543	1·05 (0·81, 1·36)	0·98 (0·74, 1·30)
Left thoracoabdominal excluded	588	0·97 (0·76, 1·25)	0·91 (0·68, 1·20)
Ivor Lewis radical lymphadenectomy	429	0·83 (0·60, 1·14)	0·90 (0·64, 1·28)
Model 3			
All patients	664	1·20 (0·93, 1·54)	1·04 (0·79, 1·37)

Values in parentheses are 95 per cent confidence intervals. Model 1, crude data; model 2, adjusted for age, tumour stage, tumour grade, chemotherapy response and lymphovascular invasion; model 3, adjusted as per model 2 plus margin status and lymph node yield.

lymph node yield (*Table 2*, model 3) a benefit for THO was seen, although the higher HR point estimate in the TTO group was not statistically significant (HR 1·20, 0·93 to 1·54). TTO showed a greater median lymph node yield (20 *versus* 13 in the THO group; $P < 0·001$), but overall rates of clear CRM involvement were similar (59·9 and 58·9 per cent respectively) (*Table 1*), albeit unadjusted for the discrepancies in T category. Analysis of the subsets of patients with T3–4 tumours indicated that clear margins were more often achieved by TTO (40·2 per cent *versus* 30·4 per cent for THO; $P = 0·065$).

In stratified analyses of patients with adenocarcinoma, no difference was seen between the operative approaches for overall survival (HR 1·05, 95 per cent c.i. 0·81 to 1·36) or time to recurrence (HR 0·98, 0·74 to 1·30) (*Table 2*).

To minimize potential selection bias, whereby some patients with bulky junctional tumours were selected for the left thoracoabdominal approach, an analysis was performed excluding these patients from the TTO group. Risk of mortality (HR 0·97, 95 per cent c.i. 0·76 to 1·25) and tumour recurrence (HR 0·91, 0·68 to 1·20) remained similar (*Table 2*), although the rate of clear CRMs in the remainder of the TTO group (325 patients) increased to 65·2 per cent and the median lymph node yield increased to 24.

To see whether radicality (as opposed to surgical approach) improved outcomes, THO was compared with a selected subgroup of TTO procedures that consisted only of Ivor Lewis resections with radical lymphadenectomy as per the WECC criteria[9]. This 'radical TTO' group of 166 patients had a median lymph node yield of 31 nodes and an R0 resection rate of 80·3 per cent, both of which were statistically higher than values in the THO group ($P < 0·001$). This did not translate into a significant difference in survival (HR 0·83, 95 per cent c.i. 0·60 to 1·14) or time to recurrence (HR 0·90, 0·64 to 1·28) (*Table 2*).

Table 3 Multivariable analysis of transhiatal (reference) *versus* transthoracic oesophagectomy for oesophageal cancer in relation to time to death and time to recurrence, stratified by tumour location, tumour category and node category

	Model	*n*	Hazard ratio	
			Time to death	Time to recurrence
Tumour location				
Oesophagus	1	175	1·61 (0·95, 2·75)	1·52 (0·86, 2·71)
Oesophagogastric junction				
Type 1	1	261	1·21 (0·87, 1·67)	1·21 (0·84, 1·74)
Type 2	1	228	1·58 (1·12, 2·23)	1·45 (0·98, 2·13)
Oesophagus	2*	175	1·01 (0·53, 1·95)	0·93 (0·46, 1·85)
Oesophagogastric junction				
Type 1	2*	261	1·09 (0·75, 1·58)	1·02 (0·67, 1·56)
Type 2	2*	228	1·04 (0·70, 1·55)	0·80 (0·51, 1·26)
Tumour category				
T0–2	1	335	1·36 (0·95, 1·94)	1·38 (0·91, 2·09)
T3–4	1	329	1·04 (0·79, 1·36)	0·95 (0·71, 1·27)
T0–2	2†	335	1·16 (0·78, 1·72)	1·28 (0·81, 2·01)
T3–4	2†	329	1·08 (0·80, 1·46)	0·95 (0·69, 1·31)
Node category				
N0	1	315	1·01 (0·67, 1·51)	1·29 (0·80, 2·07)
N1	1	145	1·22 (0·81, 1·84)	1·09 (0·69, 1·73)
N2	1	120	1·38 (0·88, 2·17)	1·27 (0·78, 2·06)
N3	1	84	1·70 (1·02, 2·84)	1·42 (0·84, 2·39)
N0	2†	315	1·03 (0·66, 1·61)	1·43 (0·86, 2·37)
N1	2†	145	0·79 (0·49, 1·28)	0·80 (0·46, 1·38)
N2	2†	120	1·15 (0·69, 1·91)	0·87 (0·50, 1·53)
N3	2†	84	2·21 (1·25, 3·91)	1·59 (0·90, 2·79)

Values in parentheses are 95 per cent confidence intervals. Model 1, crude data; model 2, adjusted for *age, tumour category, tumour grade, chemotherapy response and lymphovascular invasion, and †age, tumour grade, chemotherapy response and lymphovascular invasion.

No significant differences in survival or recurrence were encountered in subgroup analyses of more specific tumour location, T or N category, except for the N3 subgroup where there was a significant benefit for THO (*Table 3*).

Discussion

This study revealed no difference in overall survival or time to tumour recurrence between THO and TTO after adjustment for relevant confounding factors. Subgroup analysis did not demonstrate any particular characteristics that would select patients for extended resection (TTO). In-hospital mortality and hospital stay were reduced

after THO, but only the difference in hospital stay was statistically significant.

Some methodological issues deserve attention. In contrast to the majority of other published studies, this study assessed surgical approach within the context of perioperative chemotherapy in patients deemed suitable for multimodality treatment. However, it was not conducted as a randomized trial, reflected by some differences between the two groups, including stage at presentation and the proportion of patients receiving neoadjuvant chemotherapy. Although these features were taken into consideration in the multivariable analysis, this does not eliminate other sources of bias. It was not possible to eliminate variations in practice and case mix between the two units, or standardization regarding surgical technique, a problem encountered even in randomized trials that have examined radicality in upper gastrointestinal cancer surgery[11,12]. This was offset by the fact that only three surgeons performed or supervised all of the operations, that management principles were similar between the units, and there were no differences in outcomes.

The similarity in overall survival and tumour recurrence between THO and TTO in the present study might be taken to reflect the biology of oesophageal cancers with their propensity for systemic dissemination negating the potential benefits of more radical surgery. It may also reflect the pattern of node involvement for adenocarcinomas of the oesophagus or oesophagogastric junction, which is most commonly to the perigastric and lower mediastinal lymph nodes[13], areas that are dealt with equally by both approaches. Wider lymph node involvement might then be viewed as equivalent to systemic disease, unlikely to be influenced by a specific surgical approach. Systemic chemotherapy may also nullify some of the potential advantages of radical surgery by reducing positive CRM rates and effectively treating lymph node micrometastases[14,15].

Few randomized clinical trials have directly addressed the question of whether surgical approach affects outcome[1,2]. The most recent trial[2], which excluded patients receiving neoadjuvant therapy, showed lower morbidity following THO, but no significant difference in overall survival. Subgroup analysis suggested a role for more radical surgery in patients with a low lymph node burden (1 to 8 lymph nodes involved) and in those with oesophageal as opposed to junctional cancers[2]. The trial was, however, underpowered to assess these features. The relevance of a surgery-alone trial in the context of modern multimodality treatment regimens is debatable.

Three further small randomized trials, three meta-analyses and other large series have failed to demonstrate any significant survival advantage for more radical surgery[16–23]. The question of whether TTO results in greater morbidity is also debatable, particularly as complications are often poorly defined[24]. The Dutch randomized trial[1] suggested higher rates of respiratory complications after TTO, as did two of the meta-analyses[21,23] and a large population-based study from the USA[16], although other studies[18,19,22] found no differences, and particular complications, such as anastomotic stricture and recurrent laryngeal nerve injury, seem more common after THO[21].

Although some studies[9,25,26] have suggested a survival benefit with increased lymph node yield, this was not supported by the present study. Recommendations for adequacy of lymphadenectomy according to tumour T category[9] may have some merit, particularly in mitigating against the stage migration effect[27,28]. For the patient who is truly node-negative there is unlikely to be survival benefit from the extensive removal of normal lymphatic tissue, and for those with a high burden of lymph node involvement, who are likely to have systemic disease, surgical radicality is unlikely to extend survival greatly[29].

Two challenging groups are patients with micrometastases and those with a low volume of lymph node involvement. Whether a proportion of these patients might be cured or have a lower risk of local recurrence with more radical lymphatic dissection remains controversial. The present results suggest that this is not the case. Subgroup analysis showed no benefit for TTO in patients with N0 status, a group for which as many as 34 per cent might have evidence of lymph node micrometastases[30]. Similarly, there was no benefit to radical surgery in the N1 subgroup, in contrast to the results of the randomized trial[2]. Most patients relapse with systemic metastases, regardless of the surgical approach.

Tumour involvement of the CRM is widely accepted as an important prognostic marker[27,28]. Rates of involvement in the present study were similar to those reported after neoadjuvant chemotherapy[31,32], using the definition of tumour cells 1 mm or less from the margin as indicating positivity. Overall rates of CRM involvement were similar between surgical approaches. The more advanced tumours were encountered in the TTO group, suggesting that radical TTO may reduce the likelihood of margin involvement, particularly in patients with T3–4 tumours. Although it is accepted that THO cannot offer the same access to the mediastinum and is, by definition, less radical than TTO, there is little evidence of standardization in the volume of perioesophageal tissue and diaphragmatic crural resection removed by two-stage procedures[33]. In theory, this lack of standardization is a confounder that undermines studies assessing surgical radicality.

As most patients in the West have distal oesophageal or junctional tumours, this local surgery can be performed equally well with both procedures; the only real difference is the extent of mediastinal lymphadenectomy and the opportunity to obtain a clear CRM for long bulky tumours with TTO. The present study implies that the number of patients who might benefit from adoption of the latter approach is small and may well be offset by survival after THO in those unfit for TTO.

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6. Tumour stage after chemotherapy (study 3)

Tumor stage after neo-adjuvant chemotherapy determines survival after surgery for adenocarcinoma of the esophagus and esophago-gastric junction

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ORIGINAL REPORT

Tumor Stage After Neoadjuvant Chemotherapy Determines Survival After Surgery for Adenocarcinoma of the Esophagus and Esophagogastric Junction

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ABSTRACT

Purpose
Neoadjuvant chemotherapy is established in the management of most resectable esophageal and esophagogastric junction adenocarcinomas. However, assessing the downstaging effects of chemotherapy and predicting response to treatment remain challenging, and the relative importance of tumor stage before and after chemotherapy is debatable.

Methods
We analyzed consecutive resections for esophageal or esophagogastric junction adenocarcinomas performed at two high-volume cancer centers in London between 2000 and 2010. After standard investigations and multidisciplinary team consensus, all patients were allocated a clinical tumor stage before treatment, which was compared with pathologic stage after surgical resection. Survival analysis was conducted using Kaplan-Meier analysis and Cox regression analysis.

Results
Among 584 included patients, 400 patients (68%) received neoadjuvant chemotherapy. Patients with downstaged tumors after neoadjuvant chemotherapy experienced improved survival compared with patients without response ($P < .001$), and such downstaging (hazard ratio, 0.43; 95% CI, 0.31 to 0.59) was the strongest independent predictor of survival after adjusting for patient age, tumor grade, clinical tumor stage, lymphovascular invasion, resection margin status, and surgical resection type. Patients downstaged by chemotherapy, compared with patients with no response, experienced lower rates of local recurrence (6% *v* 13%, respectively; $P = .030$) and systemic recurrence (19% *v* 29%, respectively; $P = .027$) and improved Mandard tumor regression scores ($P < .001$). Survival was strongly dictated by stage after neoadjuvant chemotherapy, rather than clinical stage at presentation.

Conclusion
The stage of esophageal or esophagogastric junction adenocarcinoma after neoadjuvant chemotherapy determines prognosis rather than the clinical stage before neoadjuvant chemotherapy, indicating the importance of focusing on postchemotherapy staging to more accurately predict outcome and eligibility for surgery. Patients who are downstaged by neoadjuvant chemotherapy benefit from reduced rates of local and systemic recurrence.

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INTRODUCTION

Preoperative chemotherapy has become established in the treatment of most patients with resectable esophageal cancer in the United Kingdom after a survival benefit was demonstrated in large randomized controlled trials.[1-3] The potential benefits of preoperative chemotherapy include downstaging of the primary tumor, facilitating complete surgical resection, and treating systemic micrometastases.[4,5] If one adopts the philosophy that a high proportion of newly diagnosed esophageal cancers have occult metastatic disease at initial presentation, it follows that systemically delivered therapy might be a critical factor in altering the long-term prognosis when combined with surgery.

However, the absolute benefit of neoadjuvant chemotherapy remains relatively low. In two of the more contemporaneous trials, the absolute improvement in survival was less than 15%, and therefore, most patients did not benefit from optimal chemotherapy.[1,3] Identification of these patients would represent significant clinical progress and could potentially herald patient-specific management.

The aim of this study was to assess the long-term outcomes of an unselected population of patients undergoing preoperative chemotherapy for

esophageal adenocarcinoma. Our primary hypothesis was that the tumor stage after neoadjuvant chemotherapy would determine survival rather than the tumor stage at presentation. We also aimed to assess to what extent patients with esophageal or esophagogastric junction adenocarcinoma who are downstaged by neoadjuvant chemotherapy experience improved survival compared with patients who are not downstaged.

METHODS

Patients

A prospectively collected database between the years 2000 and 2010 consisting of 680 consecutive resections for esophageal or esophagogastric junction (Siewert type I or II[6]) tumors was used. The database represents a collaboration between two high-volume institutions for esophageal cancer in London, United Kingdom (St Thomas' Hospital and Royal Marsden Hospital).

Among the 96 patients excluded from this cohort were 15 patients who underwent surgery for benign disease, one patient without histology, and 80 patients with squamous cell carcinoma of the esophagus. Therefore, the final study cohort consisted of 584 patients with adenocarcinoma of the esophagus or esophagogastric junction. Of these, 400 patients (68%) underwent preoperative chemotherapy, whereas the remaining 184 patients (32%) underwent surgery alone.

Tumor Staging

All patients were discussed in a specialist upper GI multidisciplinary team meeting and underwent a standard protocol of investigation that included endoscopy, computed tomography (CT), endoscopic ultrasound (EUS), and latterly fluorodeoxyglucose positron emission tomography (FDG-PET). Each patient was allocated a tumor stage (cTNM) before commencement of neoadjuvant chemotherapy as decided by the multidisciplinary team. After neoadjuvant chemotherapy, patients were restaged using CT (thorax, abdomen, and pelvis), but not routinely using endoscopy, EUS, or fluorodeoxyglucose PET. All patients underwent definitive resection and, therefore, had final tumor histology available for comparison (ypTNM), and analyzed by a member of a team of dedicated upper GI histopathologists. This pathologic stage was determined using the seventh edition of the American Joint Committee on Cancer TNM staging system.[7] Downstaging was defined as a reduction in T stage or N stage of pathologic staging (ypTNM) compared with clinical staging (cTNM). Pathologic tumor regression used a categorical scale between 1 (complete pathologic response) and 5 (no response) as originally described by Mandard.[8]

Clinical Management

During the study period from January 1, 2000, to December 31, 2010, chemotherapy practice in the United Kingdom evolved rapidly. After the successful completion of a large multicenter randomized trial,[2] two cycles of preoperative cisplatin and fluorouracil became the standard treatment of resectable esophageal cancer. A second United Kingdom–based randomized trial was published in 2006, in which patients received three cycles of preoperative epirubicin, cisplatin, and fluorouracil (ECF), followed by three cycles of the same regimen postoperatively.[1] In 2008, the final results of a further randomized trial were published in which fluorouracil was safely replaced by the oral fluoropyrimidine capecitabine, and hence, epirubicin, cisplatin, and capecitabine largely replaced ECF.[9]

Thresholds for chemotherapy were also lowered over the 10-year period, initially including all patients staged as having T3 tumors or involved lymph nodes. Later (since 2005), patients staged at T2N0 were also considered for neoadjuvant chemotherapy. This group of patients from the initial period of study who did not meet the criteria for neoadjuvant therapy and patients who were not administered chemotherapy for medical reasons or personal choice were used as a control group. It was never the intention of the this study to specifically compare chemotherapy regimens, but rather to analyze the overall effects of neoadjuvant chemotherapy on outcomes. The surgical approach consisted of transhiatal or transthoracic esophagectomy, primarily dictated by individual surgeon preference.

Statistical Analysis

Descriptive statistics were used to present demographics and oncologic outcomes. Survival analysis was performed using the Kaplan-Meier method and log-rank test, and $P < .05$ was used to determine statistical significance. Survival was calculated from the date of surgery. The Fisher's exact test and χ^2 test were used to assess categorical variables, whereas the *t* test and Mann-Whitney *U* test were used to analyze continuous variables.

Cox proportional hazards models were used to calculate hazard ratios (HRs) with 95% CIs for the association between tumor downstaging (study exposure) and the two main study outcomes, overall and disease-free survival. Crude (model 1) and adjusted (model 2) analyses were performed. The prognostic markers adjusted for in the multivariable model included patient age (continuous), clinical tumor stage (T1/2N0, T1/2N+, T3/4N0, or T3/4N+), tumor grade (well, moderately, or poorly differentiated), lymphovascular invasion (yes or no), resection margin status (R0 or R1), and surgical resection type (transhiatal or transthoracic esophagectomy). Pathologic tumor stage and Mandard tumor regression scores were excluded from the model because these parameters also reflect tumor response to chemotherapy and would have confounded the model. To evaluate the proportional hazards assumption, the correlation was calculated between Schoenfeld residuals for the covariates and the ranking of individual treatment failure times. Furthermore, we also used a graphical approach to compare log-log survival curves. The proportional hazards assumption was met. Data management and analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC). Ethical (institutional review board) approval was granted for use of the database.

RESULTS

Patient Characteristics

Of the 584 patients included, the mean age was 63 years (range, 28 to 83 years), with a majority of patients being men (86%). Demographics and staging data of the study participants are listed in Table 1. In-hospital mortality was 2.5%, and the median length of hospital stay was 15 days. Overall survival of the cohort was 80% and 45% at 1 and 5 years, respectively.

Surgery consisted of transhiatal (n = 232) and transthoracic (n = 353) esophagectomy. Three surgeons performed or supervised all of the operations, and there were no differences in mortality or survival according to individual surgeon or unit performing the surgery. Overall R0 resection rate was 60%, using the Royal College of Pathologists criteria of a positive margin (ie, tumor at or within 1 mm of the circumferential resection margin).[10] This was equivalent to an 87% R0 resection rate using the American College of Pathologists definition.[7] Median lymph node yields in the downstaged and nondownstaged groups were 19 and 18 lymph nodes, respectively ($P = .7741$)

The predominant chemotherapy regimens included cisplatin and fluorouracil (n = 57), ECF (n = 218), and epirubicin, cisplatin, and capecitabine (n = 112), which accounted for 387 (96%) of the 400 patients who underwent neoadjuvant chemotherapy. The majority of patients (n = 380; 95%) were administered two, three, or four cycles of neoadjuvant treatment. The chemotherapy regimen did not significantly affect the likelihood of tumor downstaging ($P = .6665$)

Downstaging Effect of Chemotherapy

In the group receiving neoadjuvant chemotherapy, 175 patients (44%) benefitted from a downstaging effect. This group of responders, compared with nonresponders, had improved rates of clear surgical

Table 1. Demographics and Clinical Characteristics According to Neoadjuvant Chemotherapy Administration in Patients Undergoing Surgery for Esophageal Adenocarcinoma

Characteristic	No Chemotherapy		Chemotherapy (downstaged)		Chemotherapy (not downstaged)		*P*
	No. of Patients	%	No. of Patients	%	No. of Patients	%	
Total patients	184	31.5	175	30.0	225	38.5	
Age, years							.7735*
Mean	64		62		61		
SD	9		10		9		
Range	34-83		28-81		33-78		
Sex							.1545
Male	159	86.4	155	88.6	188	83.6	
Female	25	13.6	20	11.4	37	16.4	
Tumor location							.2397
Esophageal	49	26.6	25	14.3	22	9.8	
Type I EGJ	79	42.9	72	41.1	108	48.0	
Type II EGJ	56	30.4	78	44.6	95	42.2	
Histology							< .001
Adenocarcinoma	156	84.8	148	84.6	225	100.0	
HGD	28	15.2	0	0.0	0	0.0	
CPR	0	0.0	27	15.4	0	0.0	
Tumor stage (clinical)							< .001
T0N0	33	17.9	0	0.0	0	0.0	
T1-2N0	85	46.2	4	2.3	7	3.1	
T1-2N1-3	11	6.0	11	6.3	28	12.4	
T3-4N0	22	12.0	18	10.3	50	22.2	
T3-4N1-3	33	17.9	142	81.1	140	62.2	
Tumor stage (pathologic)							< .001
T0N0	28	15.2	27	15.4	0	0.0	
T1-2N0	70	38.0	59	33.7	5	2.2	
T1-2N1-3	34	18.5	51	29.1	28	12.4	
T3-4N0	16	8.7	36	20.6	25	11.1	
T3-4N1-3	36	19.6	2	1.1	167	74.2	
Tumor grade (differentiation)							.0138
HGD	28	15.2	0	0.0	0	0.0	
Well	18	9.8	9	5.1	2	0.9	
Moderate	94	51.1	101	57.7	120	53.3	
Poor	44	23.9	65	37.1	103	45.8	
Surgical resection							.0323
Transhiatal	118	64.1	59	33.7	54	24.0	
Transthoracic	66	35.9	116	66.3	171	76.0	
Lymph node yield, No.							.7741†
Median	15		19		18		
Q1-Q3	9-20		12-28		12-29		
Range	0-61		4-73		0-75		
Chemotherapy regimen							.6665
CF	—	—	29	16.6	28	12.4	
ECF	—	—	94	53.7	124	55.1	
ECX	—	—	46	26.3	66	29.3	
Other	—	—	6	3.4	7	3.1	
Chemotherapy response							< .001
Complete	—	—	27	15.4	0	0.0	
Good	—	—	12	6.9	3	1.3	
Moderate	—	—	64	36.6	53	23.6	
Poor	—	—	41	23.4	103	45.8	
No response	—	—	18	10.3	35	15.6	
Unknown response	—	—	13	7.4	31	13.8	
Lymphovascular invasion							< .001
Negative	117	63.6	132	75.4	70	31.1	
Positive	67	36.4	43	24.6	155	68.9	

(continued on following page)

Table 1. Demographics and Clinical Characteristics According to Neoadjuvant Chemotherapy Administration in Patients Undergoing Surgery for Esophageal Adenocarcinoma (continued)

Characteristic	No Chemotherapy		Chemotherapy (downstaged)		Chemotherapy (not downstaged)		*P*
	No. of Patients	%	No. of Patients	%	No. of Patients	%	
Margin status							< .001
R0	127	69.0	130	74.3	91	40.4	
R1	57	31.0	45	25.7	134	59.6	
Recurrence during follow-up							< .001
No recurrence	133	72.3	111	63.4	88	39.1	
Locoregional	17	9.2	11	6.3	30	13.3	
Metastases	21	11.4	34	19.4	66	29.3	
Both	13	7.1	19	10.9	41	18.2	
In-hospital death							.7622‡
No	179	97.3	171	97.7	218	96.9	
Yes	5	2.7	4	2.3	7	3.1	
Hospital stay, days							.7343†
Median	15		16		16		
Q1-Q3	12-22		12-24		13-23		
Range	7-78		7-101		7-191		

NOTE. *P* value refers to χ^2 comparison of chemotherapy (downstaged) versus chemotherapy (not downstaged).
Abbreviations: CF, cisplatin and fluorouracil; CPR, complete pathological response; ECF, epirubicin, cisplatin, and fluorouracil; ECX, epirubicin, cisplatin, and capecitabine; EGJ, esophagogastric junction; HGD, high-grade dysplasia; Q, quartile; SD, standard deviation.
*t test.
†Mann-Whitney *U* test.
‡Fisher's exact test.

resection margins (R0: 74% *v* 40%, respectively; $P < .001$) and lower rates of isolated local recurrence (6% *v* 13%, respectively; $P = .03$). The responders also experienced lower rates of systemic metastatic recurrence compared with nonresponders, both alone (19% *v* 29%, respectively; $P = .027$) and in combination with locoregional recurrence (30% *v* 48%, respectively; $P = < .001$). The majority of downstaged patients had evidence of pathologic response to neoadjuvant chemotherapy (Mandard tumor regression score of 1 to 4 in 144 of 162 patients; 89%). This group of downstaged patients had significantly improved Mandard tumor regression scores compared with patients who were not downstaged ($P < .001$).

In patients undergoing primary surgery, clinical staging was accurate in 78% of patients (correctly staged, n = 144 [78%]; understaged, n = 30 [16%]; overstaged, n = 11 [6%]). However, postchemotherapy staging did not discriminate between patients who achieved a response to chemotherapy and those who did not (CT showing response to chemotherapy: downstaged, 59%; not downstaged, 61%; $P = .86$).

Survival Analysis

The multivariable adjusted Cox regression analysis revealed that tumor downstaging (HR, 0.49; 95% CI, 0.35 to 0.68), lymphovascular invasion (HR, 1.88; 95% CI, 1.39 to 2.55), and positive (R1) resection margin (HR, 1.69; 95% CI, 1.27 to 2.25) were independent markers of overall and disease-specific survival, whereas patient age (HR, 1.01; 95% CI ,0.99 to 1.03) and surgical resection type (HR, 1.11; 95% CI, 0.83 to 1.49) were not (Table 2). In patients staged as cT3/4N+ who benefitted from a downstaging effect from chemotherapy, the 5-year survival was significantly improved compared with the corresponding nondownstaged group (52.5% *v* 12.6%, respectively; $P < .001$; Appendix Fig A1, online only).

Figures 1 to 4 represent a more detailed survival analysis of the patients initially staged at cT3/4N+ who proceeded to chemotherapy and were downstaged to ypT0N0 (Fig 1), ypT1/2N– (Fig 2), ypT1/2N+ (Fig 3), or ypT3/4N– (Fig 4). In each survival graph, the two control curves represent stage-matched patients who were not administered neoadjuvant chemotherapy (pTNM) and patients who were not downstaged by chemotherapy (ie, the nonresponders who were still ypT3/4N+ after surgical resection). In all of these survival analyses, a significant survival benefit was seen in the chemotherapy responders versus nonresponders ($P < .001$), and there was no difference observed between the responders and stage-matched controls.

DISCUSSION

This study indicates that the established local downstaging effect of neoadjuvant chemotherapy in resectable esophageal adenocarcinoma is also associated with a reduced systemic relapse rate and an overall improvement in survival that is independent of other known prognostic factors. Patients who had downstaging of their primary tumor after chemotherapy had survival comparable to that of patients with equivalent early-stage tumors who did not require chemotherapy. Thus, tumor stage after neoadjuvant chemotherapy seems to be more important than initial stage at presentation in terms of assessing prognosis.

Some methodologic issues deserve attention. This study allowed for the long-term follow-up of a large cohort of patients undergoing neoadjuvant chemotherapy and surgery for esophageal cancer. To the best of our knowledge, no previous study has been able to quantify the local and systemic downstaging effects of systemic therapy in this

Table 2. Crude and Adjusted Analysis Analyzing the Impact on Tumor Downstaging After Neoadjuvant Chemotherapy in Patients Undergoing Surgery for Esophageal Adenocarcinoma

Model and Parameter	Time to Death		Time to Recurrence	
	HR	95% CI	HR	95% CI
Model 1				
Tumor downstaged				
No	Ref		Ref	
Yes	0.37	0.28 to 0.49	0.40	0.29 to 0.54
Model 2				
Tumor downstaged				
No	Ref		Ref	
Yes	0.49	0.35 to 0.68	0.50	0.35 to 0.71
Patient age	1.01	0.99 to 1.03	0.99	0.98 to 1.01
Clinical stage (cTNM)				
cT1/2N+	Ref		Ref	
cT1/2N−	1.64	0.66 to 4.09	1.51	0.50 to 4.58
cT3/4N−	0.81	0.47 to 1.39	0.94	0.50 to 1.77
cT3/4 N+	1.40	0.89 to 2.19	1.70	0.99 to 2.90
Tumor grade (differentiation)				
Moderate	Ref		Ref	
Well	0.68	0.21 to 2.19	1.13	0.41 to 3.14
Poor	0.88	0.67 to 1.14	0.87	0.65 to 1.17
Lymphovascular invasion				
No	Ref		Ref	
Yes	1.88	1.39 to 2.55	1.75	1.27 to 2.42
Resection margin				
R0	Ref		Ref	
R1	1.69	1.27 to 2.25	1.84	1.35 to 2.51
Surgical resection				
Transhiatal	Ref		Ref	
Transthoracic	1.11	0.83 to 1.49	1.10	0.80 to 1.51

NOTE. Model 1 = crude. Model 2 = adjusted for age, tumor stage (cTNM), tumor grade, lymphovascular invasion, resection margin status (R0/R1), and surgical resection type.
Abbreviations: HR, hazard ratio; Ref, reference.

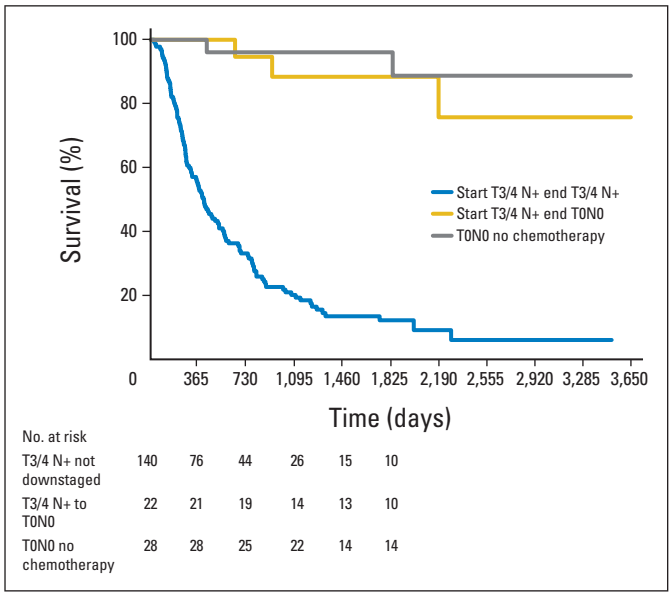

Fig 1. Comparison of surgically treated patients with esophageal adenocarcinoma, downstaged from cT3/4N+ to ypT0N0. Control groups are represented by cT3/4N+ to ypT3/4N+ (not downstaged) and T0N0 (no chemotherapy).

manner and combine it with robust long-term follow-up data. However, this trial was not designed as a randomized trial, and therefore, despite being adjusted for several potential confounding factors, it is susceptible to bias. Although two centers contributed data, staging and management principles were similar, and there were no differences in outcomes according to individual surgeon or unit of presentation. We elected to analyze patients with adenocarcinoma exclusively, to adhere to the principle of treating these tumors as distinct pathologic entities from squamous carcinomas. Failure to do so might introduce bias, an issue that has been raised in randomized controlled trials where a discrepancy in the effects of treatment has been documented between esophageal tumor subtypes.[11] Although our study contains a combination of transhiatal and transthoracic resections, surgical approach in our own data set had no impact on overall survival or disease recurrence when adjusted for relevant confounding factors.[12]

The clinical relevance of our study is that it shows that pathologic stage after chemotherapy strongly dictates prognosis, whereas the initial pretreatment staging does this only to a limited extent. This indicates that advanced diagnostic staging procedures (eg, PET-CT, EUS, or magnetic resonance imaging) should be used after neoadjuvant chemotherapy. The major clinical decision making should be based on this staging rather than the initial staging. The main purpose of the initial staging would be to identify any distant metastases (thus precluding curatively intended treatment) and to provide a baseline from which to compare response to treatment. This would be a novel clinical approach that might improve clinical decision making and survival after curatively intended treatment.

One criticism of the this study is the use of pathologic stage as a surrogate for postchemotherapy stage. Clearly, the use of imaging modalities to predict stage after chemotherapy would best inform prospective management. However, this study was intended as proof of concept, to identify the mechanism of benefit after chemotherapy

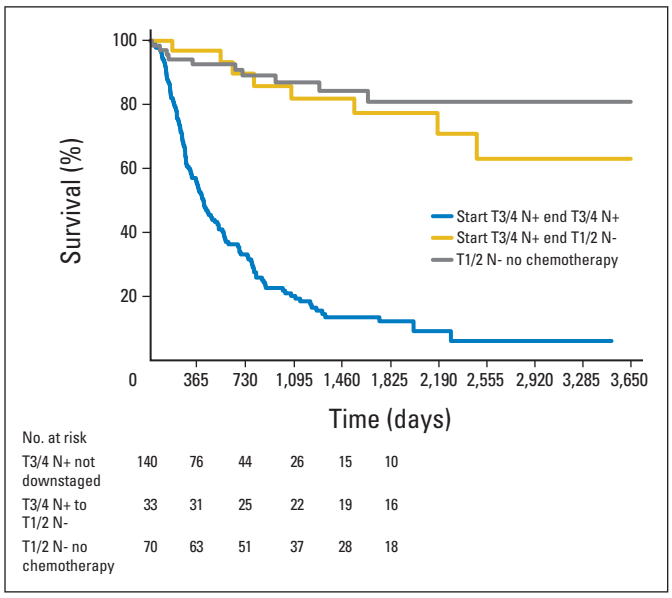

Fig 2. Comparison of surgically treated patients with esophageal adenocarcinoma, downstaged from cT3/4N+ to ypT1/2N–. Control groups are represented by cT3/4N+ to ypT3/4N+ (not downstaged) and T1/2N– (no chemotherapy).

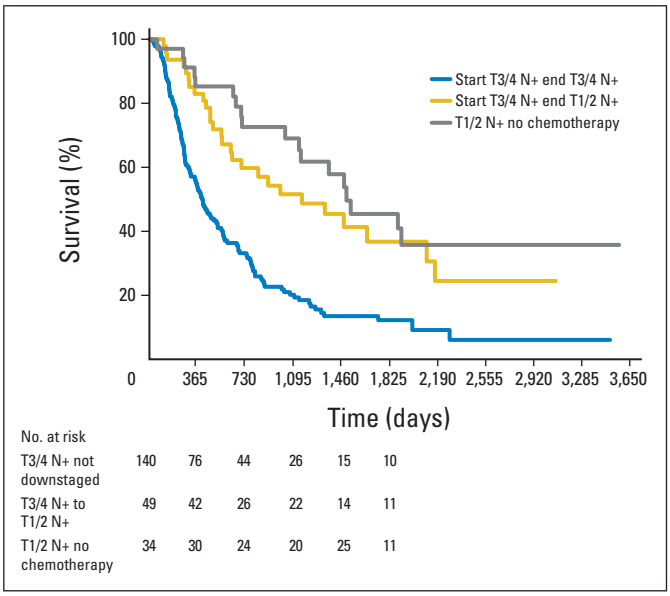

Fig 3. Comparison of surgically treated patients with esophageal adenocarcinoma, downstaged from cT3/4N+ to ypT1/2N+. Control groups are represented by cT3/4N+ to ypT3/4N+ (not downstaged) and T1/2N+ (no chemotherapy).

and attempt to quantify such benefit in a practical way. In doing so, the use of final pathologic stage to define responders is inherently more accurate. We have been able to show that a patient presenting with a T3N2 tumor who is downstaged to a T1N0 tumor has equivalent survival to a patient who was T1N0 from the outset. This simple philosophy has practical value as we aim to select patients for surgery but is fundamentally reliant on our ability to accurately stage patients before and after chemotherapy.

We have attempted to address the two alternative explanations for our study's finding that tumor downstaging is of critical importance to the outcome of these patients. The first is that the patients labeled as downstaged were simply overstaged at presentation. Although this may conceivably account for a small proportion of the benefit seen in our study, the literature would suggest that staging investigations have a tendency to understage disease rather than overstage it, a trend borne out by our control group of patients undergoing surgery alone. These patients were accurately staged in 78% of cases and overstaged in only 6% of cases. Given the magnitude of benefit seen with chemotherapy downstaging, it is difficult to comprehend that such infrequent overstaging could significantly impact on the overall results of our study. Furthermore, the fact that our downstaged patients experienced significantly improved Mandard tumor regression scores suggests validity in the selection of this group. Finally, the argument that the downstaged patients could represent a cohort with favorable tumor biology is mitigated by the fact that tumor downstaging was the most significant independent prognostic factor in the multivariable model that adjusted for these features.

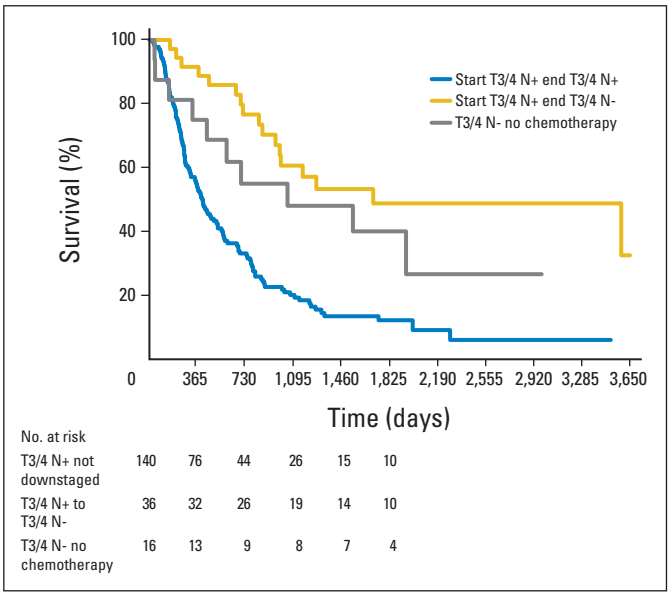

Fig 4. Comparison of surgically treated patients with esophageal adenocarcinoma, downstaged from cT3/4N+ to ypT3/4N–. Control groups are represented by cT3/4N+ to ypT3/4N+ (not downstaged) and T3/4N– (no chemotherapy).

The finding that a patient's survival might be determined by his or her stage after neoadjuvant chemotherapy lends strength to the argument that patients who respond to chemotherapy can still be successfully considered for radical treatment, regardless of the initial locoregional stage of disease. However, patients who did not respond to chemotherapy actually experienced worse survival than patients of equivalent stage who underwent primary surgery. It is logical that persisting with ineffective chemotherapy in this scenario serves no benefit, while adding to the overall morbidity of treatment.

These results highlight the potential importance of tailoring therapy to the individual patient. Such algorithms could include prolonged systemic therapy in patients who are responding well to treatment, intensifying neoadjuvant treatments (eg, adding radiotherapy to chemotherapy) in those with locally unfavorable tumors (eg, threatened surgical margins), or diverting carefully selected patients to early surgery in the absence of a response to induction therapy. Some patients who continue to have poor prognostic features after chemotherapy may not benefit from surgery at all. A prerequisite for adopting this tailored approach is the ability to measure response to neoadjuvant chemotherapy accurately. Unfortunately, there are no validated predictive molecular markers for response to chemotherapy. Pathologic tumor regression may be associated with improvements in survival,[8] but this is not commonly used to inform pre- or postoperative decision making regarding therapy. CT imaging is notoriously inaccurate at measuring response to chemotherapy, and although the addition of PET and EUS may improve restaging accuracy, these limitations currently preclude individualized therapy.[13]

The benefits of neoadjuvant chemotherapy in terms of local downstaging have been previously documented.[4] Our results concur with this, showing that a significant proportion of patients achieve a reduction in stage, which translates into improved survival, improved surgical resection rates, and reduced locoregional recurrence.

What is considerably more debatable is whether and to what extent chemotherapy has an additional systemic effect.[5] If the answer to this question is no, then it would seem logical to treat all patients with chemoradiotherapy because this would result in higher rates of pathologic response and complete resection of the primary tumor and surrounding lymphatics.[11,14] However, there are concerns that the lower radiosensitizing dose of systemic chemotherapy that such treatment entails is unlikely to provide equivalent systemic treatment

effects. Moreover, the evidence for underlying systemic micrometastases at the time of surgery for esophageal cancer is compelling.[15] The overwhelming majority of patients, including even those with a complete pathologic response after chemoradiotherapy, still die of metastatic disease.[16-18] A significant proportion of patients with N0 tumors will have evidence of lymph node micrometastases when additional pathologic analysis is performed, exceeding 30% in some studies.[19-22] Bone marrow aspirates have also shown that up to 60% of patients undergoing esophageal cancer surgery have malignant cells in the circulation.[15,23] In the absence of a systemic effect of treatment, all of these patients would presumably die of their disease.

The benefits of neoadjuvant chemotherapy for responding patients in our study are convincing, with a 57% reduction in the risk of cancer recurrence and death demonstrated for the 44% of patients who were downstaged. This benefit is significantly greater than the relative risk reduction demonstrated in the relevant clinical trials,[1-3] which take into account both responders and nonresponders. Notably, the benefits of systemic chemotherapy are not limited to downstaging; we also demonstrate a concurrent reduction in the occurrence of systemic metastatic disease for responding patients, providing sound evidence for the elimination of micrometastases. We have previously reported that pathologic stage (after chemotherapy) and pathologic tumor response (Mandard tumor regression score) are independently prognostic after esophagectomy.[17] If chemotherapy only served to downstage the primary tumor, then these two parameters could not be mutually exclusive, and all of the benefit of chemotherapy would be represented by the reduced stage of disease after chemotherapy. Therefore, we believe that the benefits of downstaging are independent of, and complimentary to, pathologic tumor regression. Given the high rates of systemic recurrence in these patients and the convincing reduction in both local and systemic relapse demonstrated in our study with neoadjuvant chemotherapy, we believe that this is an appropriate treatment for such patients.

In conclusion, this study indicates that tumor stage after neoadjuvant chemotherapy determines survival in patients with adenocarcinoma of the esophagus and esophagogastric junction. The importance of tumor downstaging in terms of survival, complete surgical resection, and recurrence pattern has significant clinical implications. The demonstration of a systemic effect of chemotherapy is particularly poignant at a time when much controversy exists regarding the optimal neoadjuvant treatment strategy for these cancers. Improving the assessment of response to neoadjuvant chemotherapy is critical if we are to successfully adopt a policy of individualized therapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
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Data analysis and interpretation: Andrew R. Davies, Fredrik Mattsson, Jesper Lagergren, Nick Maisey, Elizabeth C. Smyth, Robert C. Mason
Manuscript writing: All authors
Final approval of manuscript: All authors

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Appendix

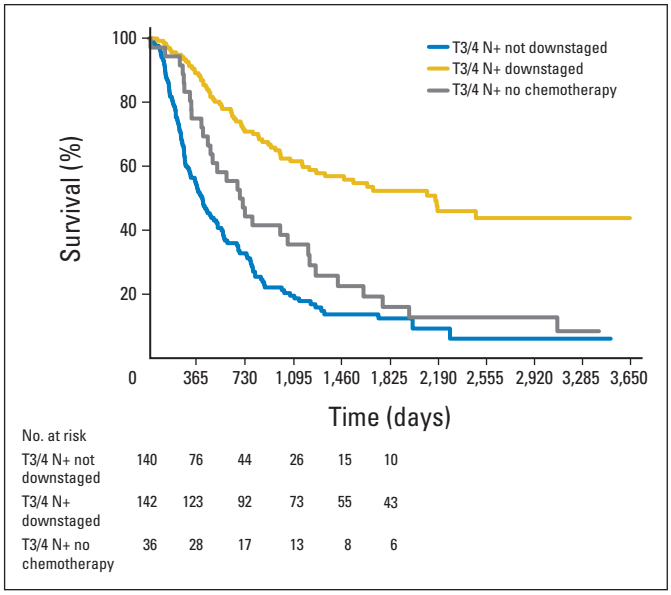

Fig A1. Survival of surgically treated patients with esophageal adenocarcinoma clinically staged (cTNM) as T3/4N+ according to administration of chemotherapy and the downstaging effect of treatment.

7. Supplementary studies

Whilst the above three studies, go some way to improving our understanding of the staging, natural history and treatment of oesophageal adenocarcinoma, in some respects they pose even more questions. All three emphasise, to a greater or lesser extent, the importance of improved staging after chemotherapy and the implications of being able to predict those patients who are not responding to neo-adjuvant chemotherapy. However, these parameters have proven to be particularly challenging despite being the subject of extensive investigation.

In an attempt to answer some of the questions highlighted by these studies, this chapter briefly presents the results of on-going studies that focus on three key areas :-

1. Validation of the ERD model proposed in study 1
2. Prediction of circumferential margin involvement – A CT based model
3. Applications of CT following NAC – the accuracy of staging, and prediction of response to chemotherapy.

7.1 Early recurrence and death after oesophagectomy : validation of a survival model

Study 1 identified locally advanced tumours (T3/4) with three or more involved lymph nodes (N2 or N3), poor differentiation, positive resection margins and poor response to chemotherapy as independent risk factors for ERD (early recurrence and death within one year of surgery). A subsequent cohort of 70 patients operated for oesophageal cancer between 2011 and 2013 i.e. in the two years following completion of study 1 was evaluated. At the time of census all patients were at least 1 year from surgery. Again, the primary outcome was early recurrence and death within 12 months of surgery.

Of the 70 patients included, 45 were alive with no signs of recurrence and 5 deceased with no recurrence at the time of death. 13 patients suffered a recurrence and died of their disease (8 of whom recurred and died within 12 months of surgery). A further 7 patients were alive at the time of census, with documented tumour recurrence.

8 patients (8/70; 11.5%) suffered ERD. Of these, 6 patients (75%) had systemic metastases. 7 (87.5%) had T3 tumours, all 8 (100%) were lymph node positive (4 N1; 4 N2/3), 7 (87.5%) had R1 resections, 6 (75%) had poorly differentiated tumours and 7 (87.5%) were Mandard 4 or 5 on pathological tumour regression assessment (the other patient had no chemotherapy).

Of the remaining patients, those with confirmed recurrence within 18 months of surgery (n=8) also displayed many of the same adverse prognostic characteristics.

The combination of a T3/4 N2/3, poorly differentiated tumour, R1 resection and Mandard score of 4 or 5 led to an 80% chance of recurrence and death within 12 months of surgery. Encouragingly, the proportion of patients suffering ERD has fallen from 17% to 12%, which may reflect improvements in staging. Advanced stage (particularly T3/4-N2/3), poor differentiation, positive resection margins and poor chemotherapy response (Mandard 4 or 5) continue to predict poor outcome, supporting the model previously described. In combination, these characteristics resulted in an unacceptably high probability of dying within 1 year of surgery.

The presence of these adverse prognostic markers should prompt a change in strategy, as these patients will never recover from surgery before succumbing to their disease. However, prediction of this group requires an accurate assessment of tumour stage following NAC and an ability to predict patients at risk of an R1 resection as well as those with a poor response to chemotherapy, all of which remain elusive.

7.2 CRM prediction model

I acknowledge the contribution of Dr. Connie Yip, who is the joint author of this, as yet unpublished, study. Dr. Audrey Jacques and Prof. Vicky Goh (Consultant GI radiologists, Guy's & St Thomas' NHS foundation trust) analysed the CT images for this study.

Predicting patients who will have CRM involvement at surgery has significant clinical applications. These patients have a poor prognosis and are at increased risk of local and systemic recurrence. Not only does an R1 resection feature in the model predicting early recurrence and death (study 1), but these patients may benefit from tailored strategies to minimise the risk of positive margins. Such strategies could include the use of neo-adjuvant CRT in certain cases and the selection of these patients for transthoracic resection, based in part on the results presented in this thesis. This study aimed to define and validate a predictive model for CRM involvement, based on contrast enhanced CT.

133 patients who underwent CT prior to surgery were studied. These post neo-adjuvant chemotherapy CT scans were reviewed by two independent radiologists and relevant radiological parameters extracted. Univariate and multivariable logistic regressions were performed. A logistic regression (LR) model and a simplified CRM_{score3} model were constructed using parameters with clinical and statistical significance: invasion of adjacent structures, circumferential aortic contact >90°, pleural thickening (IAP); longest trans-axial tumour dimension (LD) and node positivity (N+). Model performance was assessed using area under the curve (AUC) in the development (n=68) and

validation cohort (n=65). The CRM_{score3} performed as well as the LR model. Being more readily applicable to clinical practice it was evaluated for its ability to predict CRM.

In the development cohort the sensitivity, specificity, positive predictive value and negative predictive value of the CRM_{score3} was 22%, 98%, 86% and 66% respectively for those patients scoring 3.The CRM_{score3} model performed less well when applied to a separate validation cohort; however, it still had potential in identifying a group of patients with a very high risk of positive CRM.

A limitation of this model is its lack of sensitivity. The majority of patients who might benefit from intensification of neo-adjuvant therapy would not be identified with a score of 3. Lowering the threshold score to 2 reduces the specificity such that up to half of the patients would perhaps be over-treated. Clearly, more accurate prediction of CRM status would further enable a philosophy of treatment intensification for those at high risk of CRM positivity. Whether such escalation of treatment would improve outcomes in these patients remains debatable and would require a prospective trial.

Another potential criticism is the use of post-chemotherapy CT evaluation. It might be argued that the initial staging CT should be used to assess CRM risk, with neo-adjuvant treatment tailored accordingly. However, given that systemic chemotherapy has been shown to reduce CRM involvement, and the clear importance of systemic therapy demonstrated in study 3, it would be inconsistent to then suggest these patients be considered for NACRT from the outset. Whilst they may be at increased risk of local recurrence by virtue of a positive CRM, they are also at a much higher risk of systemic disease. Hence the logic in treating with systemic therapy in the first instance and selecting those for escalation based on post chemotherapy CRM status.

Thus only patients who are likely to gain a local benefit from CRT are recommended for this treatment and none are disadvantaged by sub-optimal systemic therapy. In suggesting this algorithm, it is accepted that there is currently no prospective evidence in favour of this approach, which would be a pre-requisite to implementing such a strategy.

In summary, this study constructed and validated a simple CT-based CRM predictive model which could be used to identify patients at risk of a positive CRM in standard clinical practice. The model incorporates a combination of three radiological parameters which are easily identified on routine CT assessment. Although it has the potential to impact on clinical decision making, further refinements are needed to improve the accuracy of the model to the extent that it could be prospectively studied as a decision making tool.

7.3 The accuracy and application of CT imaging following neo-adjuvant chemotherapy for oesophageal cancer

Stage after chemotherapy is important prognostically, yet in the UK, minimal resources are allocated to the assessment of tumours following neo-adjuvant treatment. In most units, CT alone is used to re-stage oesophageal cancers, despite numerous studies suggesting this modality is inaccurate at doing so.

This study evaluated the use of CT staging after neo-adjuvant chemotherapy to assess the accuracy of CT staging after NAC, and the ability of CT to predict the adverse prognostic parameters identified in study 1 (namely T3/4, N2/3, R1 resection, Mandard tumour regression score of 4 or 5/5). The study cohort included 93 patients with adenocarcinomas of the oesophagus and complete staging data.

This study confirmed that re-staging after NAC with CT is often inaccurate. It is well known that CT struggles to predict T stage, particularly after chemotherapy, where the presence of fibrosis makes this interpretation difficult. In the allocation of T stage to clinically prognostic sub-groups i.e. T1-2 or T3-4, CT was accurate in 51 (55%) patients, understaged in 18 (19%) and overstaged in 24 (26%). Therefore for the prediction of T3/4 status the sensitivity, specificity, PPV and NPV of CT were 63%, 47%, 56% and 54% respectively.

TNM 7 mandates an assessment of the number of involved lymph nodes to assess “N” status. Whilst CT is reasonably accurate at making an overall assessment of whether a patient is node positive or node negative, its ability to specify the number of involved

lymph nodes is poor. This results in high rates of over-staging (26%) and under-staging (41%) of nodal status. When CT stages N2/3 disease it has a high positive predictive value, but a very low sensitivity such that only 14% of N2/3 patients would be identified. The implications of this for a model predicting ERD are that CT alone would only pick up a small proportion of patients at risk, but within that group, would do so with high levels of confidence. Ultimately, the poor sensitivity of CT supports the need for more staging information after NAC.

Encouragingly, this preliminary data support a role for CT in the assessment of response to chemotherapy. This information is important for two reasons; firstly a poor response may predict patients at high risk of ERD. Secondly, response to chemotherapy (or lack of) may in future be used to guide further treatment strategies. An assessment on CT of whether there has been a down-staging effect from chemotherapy (e.g. RECIST score) combined with a quantitative estimation of this response (% volume change) has shown significant promise, particularly at distinguishing Mandard 1-3 from Mandard 4-5 tumour regression grades (sensitivity, specificity, PPV and NPV of 79%, 62%, 76% and 66%). This is of interest, as it corresponds to the prognostic cut-offs identified by the ERD model in study 1 and other studies [47]. It also has the potential to identify the “down-staged” group, highlighted in study 3 as having a significantly improved prognosis.

Given that PET has also been shown to predict response to chemotherapy with reasonable accuracy, it would be interesting to combine the model above with a measure of biological response such as SUV reduction or tumour heterogeneity. It is conceivable that the combination of these modalities might improve accuracy further, to the point of being a clinically useful predictive tool for chemotherapy response assessment.

A logical extension of this was to evaluate whether the same parameters that predict response to chemotherapy might also predict margin status, this being the final variable required for a poor outcome (ERD) model. Whilst the lack of down-staging on CT (i.e. stable disease) and a tumour volume change of less than 50% did show some ability to identify those at risk of margin involvement, it lacked sufficient PPV to direct patient management. However, it may have potential if combined with other parameters, such as those identified in the CRM_{score3} model described above. As such, a fourth point awarded for a lack of response to chemotherapy could improve the overall performance of the model (CRM_{score4}), making it more suitable for prospective clinical evaluation.

In conclusion, CT staging after NAC is inaccurate. This modality, in isolation, is unable to provide sufficient staging detail to inform prospective decision-making, implying that further staging investigations should be considered after NAC, such as PET, EUS or MRI.

However, there may be a role for CT in predicting response to chemotherapy. Stable disease is a frequently used, yet misleading term, which implies status quo following chemotherapy is an encouraging outcome. On the contrary, “stable disease” by definition, means no appreciable improvement in the tumour, the connotations of which are entirely different when interpreting the perceived benefits of treatment. It is therefore not surprising that such patients are frequently found to have poor or no response to chemotherapy on pathological analysis. Stable disease combined with tumour volume change, may be able to predict chemotherapy response prior to surgery. Whilst CRM prediction remains challenging, the combination of the two predictive models described above may herald a clinically useful tool, one which merits further investigation.

8. Discussion

8.1 Summary of findings

The main findings of these studies are summarised below :-

- Most patients (82%) suffering early recurrence and death (ERD) following surgery for AC of the oesophagus, do so with systemic metastases.
- Prognostic features that independently predict ERD include pathological tumour stage (particularly T3/4 N2/3), poor tumour differentiation, R1 resection and poor response to neo-adjuvant chemotherapy (Mandard 4 or 5/5)
- The combination of these factors has the potential to select a group of patients with a sufficiently poor outcome, that alternative strategies to surgery should be considered. A patient who remains T3/4 N2/3 after NAC, with an R1 resection, poorly differentiated tumour and poor response to NAC has a 15% chance of surviving 18 months from surgery. This model has been validated in a subsequent cohort of patients.
- Limitations in the ability to accurately re-stage tumours after NAC and predict response to treatment, currently preclude the selection of this high risk group for alternative management strategies, and indeed any individually tailored therapy. CT in isolation is inadequate at TNM re-staging after chemotherapy.
- Models predicting CRM involvement may be achievable, thus enhancing our ability to identify this poor prognostic factor prior to surgery, and potentially facilitating a change in neo-adjuvant treatment strategy in selected patients.
- The more radical transthoracic surgery does not confer a survival benefit over the less radical transhiatal resection. Disease free survival and patterns of recurrence were also similar between operative approaches.

- Transhiatal resection resulted in a significantly reduced hospital stay and a trend towards reduced mortality compared to transthoracic oesophagectomy. These characteristics may make it particularly suitable for elderly patients or those with co-morbidities who are high risk for surgery.
- Radical transthoracic resection did increase lymph node yields and R0 resection rates, the latter most pronounced in T3/4 tumours, compared to transhiatal resection. Whilst this did not lead to improved survival, it suggests that small sub-groups may be selected for this approach.
- Tumour stage after NAC, as opposed to initial stage at presentation, strongly determines survival for AC of the oesophagus.
- Patients down-staged by NAC had significantly improved overall survival, improved R0 resection rates and reduced systemic relapse, supporting the role for NAC in both local down-staging and the elimination of micro-metastases. Down-staging was the strongest independent predictor of survival on multivariable analysis.
- The ability to accurately predict down-staging after NAC would represent significant progress and may change patient management. Resources should focus on the assessment of tumour stage after chemotherapy. In the first instance this supports the use of PET/CT before and after chemotherapy, however other modalities such as EUS and MRI may have a future role to play.
- The absence of a response to NAC on CT (i.e. stable disease), combined with a quantitative assessment of tumour volume change on chemotherapy has shown some promise in the prediction of pathological tumour regression.

8.2 Discussion

These studies have demonstrated the significant improvements in outcomes that can be achieved with a multi-disciplinary approach combined with modern investigation and treatment pathways. An in-hospital mortality rate of 2% aligned with an overall 5 year survival of 45% after oesophagectomy compares favourably to most published series [3, 206].

Early recurrence and death after oesophageal surgery is associated with certain adverse prognostic factors (advanced stage [T3/4 N2/3], poor differentiation, R1 resection, poor/no response to chemotherapy [Mandard 4/5]), the combination of which leads to a very poor outcome. These patients have an unacceptably high risk of early recurrence after surgery and should be considered for alternative oncological treatments.

Surgical approach does not seem to impact greatly on overall survival or the likelihood of recurrence. Whilst the more radical TTO may facilitate a greater lymphadenectomy and improve R0 resection rates in certain sub-groups, this did not translate into an overall survival advantage. There was a trend towards lower mortality following THO and a significantly reduced hospital stay that could be taken as a surrogate for reduced morbidity.

Stage after chemotherapy appears to be a more accurate predictor of outcome than initial tumour stage at presentation. Given its prognostic importance, the current allocation of resources to staging after chemotherapy is inadequate. In contrast, multiple investigations are used for initial tumour staging, some of which will not alter

decision-making and may be unnecessary. NAC has demonstrated ability to down-stage the primary tumour and reduce the rates of systemic recurrence, therefore supporting its role in the elimination of micro-metastases in at least some cases.

Taken together, these studies strongly support the philosophy of treating most potentially resectable oesophageal adenocarcinomas as a systemic disease. On the basis of the available evidence, neo-adjuvant chemotherapy followed by surgery should remain the mainstay of treatment for the majority of oesophageal adenocarcinomas, pending results from on-going RCTs. Predictive models that could directly guide individualised patient management are achievable but require improved staging after NAC. These could include selecting patients for specific neo-adjuvant treatment strategies, directing surgical approach in patients deemed suitable for resection and the avoidance of surgery in those who are unlikely to benefit.

Some methodological issues deserve attention. These studies utilised a large prospectively collected database of oesophageal cancer patients, rigorously cross-referenced with other available data sources to ensure accuracy. The high volume of patients, availability of long-term follow up and the use of a population that reflected real time working practice were all strengths of the database. The conclusions drawn from the analysis of this robust dataset are therefore of greater validity. However, none of the studies were conducted as randomised trials and hence, despite adjustments for known prognostic factors, were susceptible to bias from confounding. Whilst it was impossible to completely eliminate variations in practice between the two contributing units, management principles and overall outcomes were very similar between the institutions. Only three surgeons performed or supervised the surgeries, providing a consistency of surgical technique often lacking in multi-centre trials where this has been difficult to standardise. This thesis focussed on adenocarcinoma of the oesophagus and OGJ, given the extensive evidence that these tumours should be

treated as distinct pathological entities from squamous cell carcinomas. This added to the validity of our results by reducing the heterogeneity of the cohort.

All of the studies used definitive pathological stage to stratify patients after surgery. Whilst this may be considered the gold standard in terms of analysing the true stage of the tumour, this information is not available at the time of patient selection for surgery. Clearly, the ability to improve prospective decision making is reliant on staging modalities accurately predicting tumour stage after NAC. The use of clinical staging after NAC in statistical models, would have allowed for assessment of the accuracy of such modalities. However, given that staging accuracy after NAC was not the primary clinical question, this (notoriously inaccurate) stage could have acted as another confounder, and was therefore avoided.

The advantage of presenting a thesis by publication route is the acknowledgement, through peer review, of current clinical relevance in the field of oesophageal cancer surgery. Each of the three studies used a novel approach to add a new perspective to the existing literature. No study has specifically examined ERD in western patients with adenocarcinoma with a view to identifying factors that should lead to the avoidance of surgery. Whilst surgical resection type has been extensively studied, our patient numbers allowed for statistical models that examined surgical radicality in greater detail than previously performed. Additionally, this was investigated in the context of most patients undergoing peri-operative chemotherapy, whereas previous studies assessed patients undergoing surgery alone. Finally, no published study has been able to quantify the down-staging effects of NAC in a comparable way to that performed in study 3. The idea that a tumour behaves according to its stage after chemotherapy has practical value, as well as important implications for staging algorithms. With the confirmation of a systemic benefit following neo-adjuvant chemotherapy, and the

demonstration of AC as a predominantly systemic disease, it may be reasonably concluded that this is the correct strategy for most patients.

In assessing the implications and clinical relevance of the results presented in this thesis, it would be logical to approach each step in the investigation and treatment algorithm, addressing the impact of these studies on our current knowledge.

8.2.1 Initial Staging

The role of initial staging is predominantly to identify patients with metastatic disease who are not eligible for curative treatment, and to select the remainder for appropriate therapy. A curatively intended approach may include endoscopic resection or primary surgery for the earliest tumours (HGD or T1) or neo-adjuvant therapy followed by surgery in most other scenarios. This broadening of the indications for neo-adjuvant therapy over the last ten years in some ways simplifies the decision making requirements of initial staging. In patients proceeding to NAC, initial staging also needs to provide an adequate baseline from which to compare response to treatment.

Currently most patients undergo a CT at diagnosis followed by EUS and PET, with additional laparoscopy performed for junctional tumours. Given the improvements in PET imaging and the ability to combine this with contrast enhanced CT (i.e. PET/CT), the need for separate CT and PET investigations will probably diminish in the future. The anatomical and physiological correlation afforded by PET/CT may actually provide sufficient local staging information to make most initial decisions, and thus EUS may become redundant in most patients. Notable exceptions to this may be the selection of early tumours for endoscopic therapy or locally advanced tumours, which may be rendered unresectable by tumour invasion of surrounding structures. EUS could be performed on a selective basis in these patients. The withdrawal of EUS from the standard investigation algorithm would place more demands on the reporting of PET/CT, particularly in the evaluation of nodal status, in order to comply with the requirements of TNM 7. It remains to be seen whether PET/CT can provide comparable accuracy to EUS in this specific setting.

The literature would also suggest that PET/CT is accurate in the detection of metastases. Given that the justification for additional laparoscopy was based on

historical data that utilised CT alone, laparoscopy may nowadays be unnecessary in most patients with oesophageal or OGJ AC.

With the demonstration that tumour stage after chemotherapy is the major determinant of survival, more important prognostically than initial tumour stage at presentation, it may be that the only staging investigation required in the majority of patients at diagnosis is a dedicated contrast enhanced PET/CT. This would allow for direct comparison with the same modality after NAC. The only reason to add further investigations at initial staging would be the finding that such modalities were useful at re-staging, and hence the desire to compare like for like, before and after chemotherapy. EUS and MRI both merit further investigation in this respect.

8.2.2 Neo-adjuvant treatment

The results of the CROSS study, a large randomised clinical trial from the Netherlands, have strengthened the argument for the use of NACRT in patients with lower oesophageal SCC. This subject was beyond the remit of this thesis which has focussed on adenocarcinoma of the oesophagus rather than squamous cell carcinoma [127].

In this same trial, however, the benefit of NACRT in adenocarcinoma did not reach statistical significance against a surgery alone control arm. There was also no benefit for NACRT in the sub-group of patients with lymph node positive disease. Hence, the criticism of this trial was that the lower radio-sensitizing dose of chemotherapy did not show any survival benefit in the two groups of patients with the greatest chance of systemic disease, i.e. those with adenocarcinoma and positive lymph nodes. Extrapolating from studies of definitive CRT, this discrepancy between AC and SCC is consistent, with the former being less responsive to radiotherapy [28, 230].

A further study detailing the recurrence patterns of patients enrolled in the CROSS trial demonstrated the main benefit of NACRT to be a reduction in local recurrence (34% vs 14%; $p<0.001$), particularly evident in SCC patients, with a more marginal reduction in systemic metastases compared to the surgery alone group (35% vs 29%; $p=0.03$) [243]. Other studies have failed to show any systemic benefit for NACRT [244]. Given the higher rates of systemic disease with AC, and the high incidence of metastases in patients following NACRT, a logical conclusion is that such treatment does not have adequate systemic efficacy despite its excellent local control statistics.

To some extent, a similar criticism could be levelled at currently available chemotherapy regimens, as patients still die predominantly of systemic disease despite

systemic therapy. However, given the significant systemic benefit for NAC demonstrated in RCTs, supported by this thesis, and the additional morbidity of radiation, it would seem logical to treat adenocarcinoma patients with maximal systemic therapy in the first instance. This is based on the supposition that additional chemotherapy agents or higher doses of drugs made available by the omission of XRT, will have improved efficacy for micro-metastases, an issue that may be resolved by the results of on-going randomised trials.

Whether a small proportion of patients at particular risk of isolated local recurrence may be selected for intensification of neo-adjuvant treatment, i.e. the addition of radiotherapy, is unclear from the literature, as it is not possible to predict these patients prior to surgery. Logically, they are the only group who might benefit from radiation as the remainder of patients' prognoses are determined by the presence or absence of metastatic disease. Only 7% of patients in our series died with isolated local recurrence after oesophageal cancer surgery. The CROSS trial also demonstrated isolated local recurrence to be extremely rare, occurring in only 9% of patients after surgery compared to 3% after NACRT [243]. It therefore remains difficult to justify treating virtually all patients with XRT in order to conceivably benefit only a small minority.

The use of a surrogate for high risk of local recurrence, such as a predictive model for circumferential margin (CRM) involvement (R1 resection), has shown some promise in our data. As the model is based on post-chemotherapy CT, patients would receive systemic therapy initially with the perceived systemic benefit of such treatment and the possibility of local down-staging. However, those still at high risk of a positive CRM could be escalated to CRT in an attempt to improve local control prior to resection. Whilst this strategy may be logical, it is important to note that 70% of patients with an R1 resection in our series still died of metastatic disease, not local recurrence. Indeed,

a similar pattern has been shown in other studies examining patients with a positive longitudinal margin who might have been expected to suffer local recurrence but actually died of systemic disease [40]. These patients tend to have advanced tumours with poor biology.

Some studies have specifically looked at the intensification of neo-adjuvant treatment on an individual patient basis. The MUNICON II trial used PET to select “non-responders” to NAC (less than 35% reduction in SUV) for additional XRT [130]. Whilst the metabolic responders had clearly improved outcomes, this trial demonstrated no survival benefit for additional XRT and high rates of systemic relapse regardless of the treatment regimen. The fact that survival was similar between the non-responding groups of patients in MUNICON (non-responders diverted to surgery) and MUNICON II (non-responders diverted to NACRT then surgery) using identical criteria, implies that it is the response to chemotherapy that ultimately dictates outcome in these patients. Non-responders to chemotherapy have a poor outcome irrespective of the choice of salvage strategy. Whether different criteria for the selection of patients for NACRT, as proposed by the CRM model, would affect this overall outcome remains uncertain.

Compared to the use of “non-responders”, a predicted positive CRM may be a more logical indication for XRT as the treatment directly addresses the problem at hand i.e. an increased risk of local recurrence. The risk-benefit for additional radiation is clearly much improved in this specific group of patients than it would be in an unselected population. Whilst this algorithm would require prospective evaluation prior to implementation, it would seem intuitive given the relatively small number of patients who may conceivably benefit from such escalation, and the morbidity associated with radiotherapy. Clearly, it is also reliant on the accurate prediction of CRM status. Regardless of the criteria used to select neo-adjuvant treatment, the search for more

effective systemic therapy should remain paramount, as this will have a far greater impact on overall outcome than any measure targeting local control.

In patients who are responding to chemotherapy, there is a strong argument for completing all six cycles of treatment prior to surgery. This would allow for maximal down-staging of the primary tumour, improved surgical margin rates and the guaranteed delivery of systemic therapy. Given that half of patients in the relevant RCTs did not complete chemotherapy following surgery, and the clear demonstration that adenocarcinoma of the oesophagus recurs systemically, the rationale for maximal up-front chemotherapy is strong. The impact of prolonged chemotherapy on complication rates following surgery would have to be examined prospectively.

A major challenge is what to do with the non-responders to NAC, assuming this group can be confidently identified. Our data confirms that these patients do poorly after surgery, gaining no survival benefit whilst suffering the side-effects of treatment. It is tempting, therefore, to change strategy in the absence of a response to chemotherapy. Diverting to surgery is one option, however these patients have a high risk of systemic relapse and will have been subjected to major resection with little realistic chance of cure. Likewise, escalating to NACRT may improve local response rates, but most patients will relapse systemically and prospective trial evidence (MUNICON II) confirms no benefit to this approach. One alternative might be second-line systemic therapy, which could include chemotherapeutic or biological agents, with surgery being reserved only for responders to such treatment. However, no such option currently exists with any reasonable evidence base. Finally, it could be that diverting non-responding patients away from the surgical pathway altogether, towards definitive chemo-radiation represents the most pragmatic compromise, and one that may offer comparable survival to surgery anyway in this particular group. One challenge with this approach,

for AC at least, is that the lower response rates of these tumours to CRT guarantees that a proportion of these patients will subsequently return to the MDT meeting with residual or recurrent cancer, and an oncologist wishing to explore the options for salvage surgery. Whilst this may seem unappealing given the initial prognosis, those patients with poor biology would likely have been selected out by this approach due to the development of metastatic disease during oncological treatment. The remainder, could simply be observed on the basis that they have had their definitive treatment or, in selected cases, may be considered for salvage resection after a reasonable period of surveillance.

A pre-requisite for implementing such major changes to these treatment pathways is the ability to identify which patients are not responding to chemotherapy. Nowhere is this principle more important than in the prediction of those patients unlikely to survive 12 months from surgery. They tend to have the ominous combination of advanced tumours and minimal response to chemotherapy. As a result of being inappropriately selected for resection, they have not benefitted from surgery. However, it still remains difficult to advise a fit patient with a technically resectable tumour not to have surgery on the basis of a predicted outcome. As such, the incidence of ERD will never be zero, as this would imply that too many patients have been denied the benefit of the doubt.

8.2.3 Re-staging after chemotherapy

The assessment of response to NAC continues to represent a significant challenge. Current practice utilises multiple staging investigations at initial presentation but only CT assessment after NAC. As most studies have demonstrated this modality to be poor at re-staging, and given the clear importance of stage after NAC on survival, there remains a conspicuous discrepancy in the allocation of imaging resources to this critical point in the algorithm [72]. A minimum requirement would appear to be the use of contrast enhanced PET/CT before and after chemotherapy. As well as being the most sensitive investigation for metastatic disease, PET/CT allows for TNM re-staging combined with a measure of physiological response to treatment [245]. Newer parameters measurable by PET, such as MTV, TLG and tumour heterogeneity are only likely to improve this response assessment in the future.

There may also be some merit in comparing chemotherapy response within lymph nodes to that in the primary tumour, as there is some evidence that such response may not be proportional [50]. Although a down-staging response in regional lymph nodes may be more difficult to detect radiologically, it is arguably more important prognostically than a reduction in the size of the primary tumour. However, the evidence suggests that both sub-groups will have improved survival compared to patients exhibiting no response whatsoever [50]. Either way, it is clear that radiologists need to be challenged to be as specific as possible in their reporting of tumour stage after chemotherapy, and this should be prospectively documented as part of institutional and national dataset requirements.

Numerous studies have examined the role of EUS after NACRT for response prediction, with conflicting results. Whilst assessing T stage after chemotherapy is difficult with EUS, its role in the evaluation of nodal status following NAC is promising.

EUS with FNA has been successfully used to identify residual nodal disease after CRT (sensitivity 82%, accuracy 68%) [158]. Given that on-going N2 or N3 disease after NAC has been shown to be the strongest predictor of ERD following surgery in study 1, this could be used to justify a role for repeat EUS in high risk patients. A patient with confirmed multi-node disease after NAC is unlikely to benefit from surgery due to the high probability of occult metastatic disease. Two challenges in adopting this approach are the false positive results created by traversing the primary tumour to sample lymph nodes, and the need to sample multiple nodes in order to prove N2 or N3 disease.

The role of MRI in anatomical re-staging and response assessment following chemotherapy is unknown but has significant potential. On-going prospective studies will decide whether MRI is to be used as a niche investigation or whether it will become a mainstream staging modality that supersedes CT and potentially even PET in the future.

MRI has also shown promise in its ability to predict CRM status, akin to its role in rectal cancer [246, 247]. An R1 resection was a negative prognostic indicator in all three studies. A means of predicting CRM involvement could be important in the context of data from this thesis, and might influence decision-making in several ways :-

1. An R1 resection would be one component of a predictive model for early recurrence and death
2. A patient at risk of an R1 resection could be selected for intensification of neo-adjuvant therapy
3. A patient with an oesophageal tumour and threatened surgical margins could be selected for a transthoracic approach on the basis of an improved rate of margin clearance with this strategy.

As such, further work to improve CRM predictive modelling is justified.

Although susceptible to some degree of placebo effect, a patients' symptomatic response to chemotherapy remains an important clinical marker that should not be ignored. An improvement in swallowing, and weight gain on chemotherapy are markers of response that are arguably as sensitive as any currently available imaging modality at predicting a favourable outcome [53].

8.2.4 Tailored therapy

In patients who have received NAC, tumour stage after chemotherapy will dictate their prognosis. Patients who benefit from a down-staging effect from chemotherapy will have lower rates of R1 resection, reduced likelihood of metastatic recurrence and improved overall survival. However, patients who do not respond to NAC will have gained no benefit from treatment, yet still suffered the morbidity of chemotherapy.

Currently, patients who are resectable after 3 cycles of NAC proceed to surgery, with the majority requiring 3 further cycles of adjuvant treatment assuming they are able to tolerate such treatment. A number of scenarios exist following neo-adjuvant chemotherapy that merit consideration:-

1. Radiological CPR – Most patients will continue to surgery on the basis that radiological assessment cannot guarantee complete eradication of all tumour cells. Assuming complete response could be predicted radiologically, the benefit of surgical resection in the context of a tumour with no residual viable cancer cells is contentious. The data on patients with CPR after NACRT would suggest that 50% still suffer recurrence within 5 years of surgery. Whilst most of these develop systemic metastases, the remainder could conceivably have been prevented by surgical resection, therefore justifying this operative approach. In contrast, our data suggest that a CPR following NAC, although less commonly encountered than after NACRT, is almost synonymous with cure, resulting in a 90% 5 year survival. A prospective trial would be required to determine whether these patients gain any benefit from surgery. In the meantime, pending improvements in the radiological assessment of CPR and convincing evidence to support a conservative approach in such patients, surgical resection should still be considered in this scenario.

2. Clear evidence of down-staging – These patients have benefitted from neo-adjuvant treatment. Proceeding to surgery at this point is a very reasonable, evidence-based strategy. However, as outlined above, 40% of patients will not complete adjuvant therapy following surgery. This number is too high, for a sub-group of patients who are actually benefitting from systemic treatment. The alternative is therefore to complete all 6 cycles of chemotherapy prior to surgery, thus maximising tumour down-staging and guaranteeing the delivery of beneficial systemic therapy.

3. Disease progression to metastases – These cases unfortunately represent tumours with poor biology, such that these patients likely would have recurred early had they been treated with primary surgery.

4. A resectable tumour but poor prognostic markers (either disease progression on chemotherapy or poor initial prognostic markers with no improvement on NAC) - These patients are at very high risk of ERD, which may in future be quantifiable with prognostic modelling. Surgery should be considered with caution as these patients may be better served by definitive CRT or second line systemic therapy. This decision must be taken on an individual patient basis following discussion of the risks and benefits of each option.

5. “Stable disease” - Arguably the most challenging group. Whilst such a patient is not likely to have benefitted much from NAC, in the absence of a contra-indication to surgery, they will probably continue to resection along the current pathway. This may be one of the few scenarios where initial staging is important in assessing prognosis, given that these tumours have not been down-staged by chemotherapy. In the context of advanced initial staging, “stable disease” on imaging is very unlikely to result in cure following surgery, in a similar way to

that described above in 4. However, for earlier tumours, a poor response to chemotherapy may be an indication for resection as there is no benefit in continuing with toxic systemic therapy, and a resected early stage tumour may still offer a reasonable long term prognosis. Assuming a poor response to chemotherapy is confirmed on pathological analysis, the merits of completing adjuvant chemotherapy are far from certain. This subject requires prospective evaluation in its own right.

6. A bulky primary tumour, with no evidence of metastatic disease, but radiological features suggestive of a locally unfavourable tumour despite NAC (e.g. contact with diaphragmatic crura, pericardium or pleura). These patients have had systemic treatment but remain at high risk of an R1 resection following surgery. Some radiological evidence of response to initial chemotherapy may prompt a continuation of this treatment to six cycles i.e. primary chemotherapy. The group without a response to NAC, and predicted CRM involvement, could be individually selected for the addition of radiotherapy, with the intention of reducing this risk at surgery. A transthoracic resection may then be considered following this intensified neo-adjuvant treatment, to maximise the chance of achieving a negative margin, whilst accepting that systemic disease is still most likely to dictate outcome.

7. Advanced disease at diagnosis e.g. nodal involvement categorised as “M1” disease – Patients with advanced nodal disease outside the surgical field (e.g. aorto-caval lymph nodes at diagnosis), may increasingly be put down a primary chemotherapy route only to re-present a therapeutic dilemma by virtue of an excellent response to treatment. This increasingly common scenario, often in young patients, is one in which there is radiological resolution of the disease that originally rendered the patient unresectable and hence the debate as to whether they should be treated according to their pre-chemotherapy (M1) or

post chemotherapy (M0) stage. Undoubtedly, these patients require detailed re-staging to elicit their true post-chemotherapy stage, a process that is likely to include endoscopy, PET/CT and laparoscopy as a minimum. However, if we were to extrapolate from the results of study 3, basing treatment on the stage of disease after chemotherapy, there may theoretically be a role for resection in this carefully selected group. Clearly this would venture significantly away from a conventional treatment pathway and these patients would therefore have to be enrolled in prospective studies.

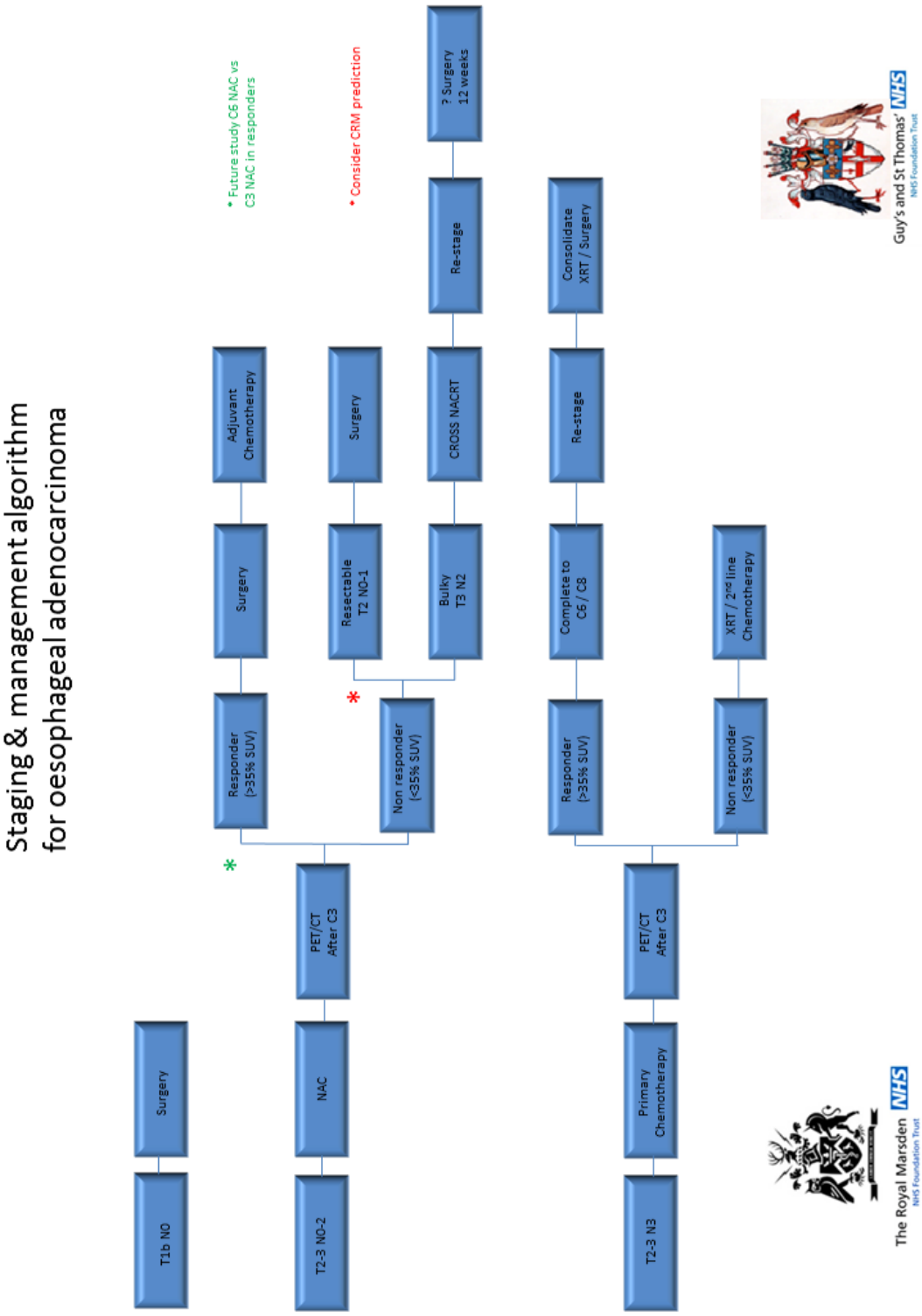

Fig. 8 *Proposed algorithm for the staging and management of oesophageal adenocarcinoma*

8.2.5 The choice of surgery

This data, and the results of numerous trials, would suggest that the choice of operation does not have a significant bearing on long term survival [208, 248, 249]. Overall, more radical surgery does not confer a survival benefit compared to less radical surgery and may increase the morbidity and mortality [4, 213] . The reasons for this presumably relate to the natural history of oesophageal cancer. Most patients have advanced disease at presentation that is incurable by surgery alone. Those with early disease have a low probability of margin involvement and lymph node metastases and hence the extensive removal of normal lymphatic tissue is unlikely to greatly extend survival. In the remainder of patients, the lymphadenectomy in the abdomen and lower mediastinum afforded by THO is likely to provide comparable oncological clearance of the lymph nodes at greatest risk of involvement. Lymph node metastases outwith this field are almost certainly a manifestation of systemic disease such that radical surgery would not influence survival in these patients.

However, some individual scenarios do merit consideration in light of the available data. An elderly or medically unfit patient, particularly with underlying respiratory disease, might reasonably be considered for THO given the equivalent overall survival and potentially reduced morbidity with this approach. This tailored strategy for transhiatal resection in high risk patients has been proposed elsewhere in the literature [250]. However, proponents of TTO might argue that the results of study 2 hardly justify a change in approach. The outcomes from TTO in study 2 exceeded historical controls. A hospital mortality of 3% dating back to 2000, with a hospital stay of 17 days represent excellent short term outcomes over this period of time. Aligned with a 5 year survival approaching 50%, these results would be considered acceptable anywhere in the world.

One further group where a selective policy may be considered is that of a younger, fit patient with a T3/4 oesophageal tumour and N1 disease on clinical staging i.e. a low number of involved lymph nodes. In this dataset, a radical TTO reduced the chance of an R1 resection in T3/4 tumours and the HR for survival favoured TTO in the N1 sub-group (albeit non-significantly). Given that the RCT also suggested that this limited node positive group may benefit from more radical surgery, this would be a reasonable strategy based on the currently available evidence.

Given the demographic shift of oesophageal cancer from mid oesophageal SCC to adenocarcinoma of the lower oesophagus and OGJ, some surgeons believe there is an expanding role for the left thoraco-abdominal approach which affords excellent access to the hiatus, particularly for bulky junctional tumours in obese patients. Whilst there is no evidence to support the use of the left chest approach over the right chest, access to the tumour is excellent, making it a useful option in selected cases.

Whilst MIO has been successfully implemented in a number of high volume institutions worldwide, it has not been uniformally accepted within UK practice, partly due to higher complication rates encountered on surgeons' learning curves [251]. The same can be said of robotic surgery [252]. The results of these techniques must be robustly audited to ensure there is no compromise in standards, in pursuit of smaller scars. That said, the potential advantages of well delivered minimally invasive surgery are overtly apparent from the worldwide literature [219].

Ultimately, of the various available operative approaches to the oesophagus and OGJ, none have been consistently shown to improve survival. The pragmatic conclusion, therefore, is that surgeons familiar with one particular technique may justifiably

continue to do so without compromising patient outcomes. Whilst there may conceivably be a role for selecting certain patients for a specific operative approach, the proportion that may benefit from this strategy is likely to be small.

8.3 Future directions

All of the steps highlighted above, mark a transition away from generic treatment pathways, towards patient specific therapy. As data become available to guide such decision making, this represents a logical progression, however it is more labour intensive requiring a greater attention to detail on behalf of clinicians and the multi-disciplinary team as a whole.

One of the intentions of the new 8th edition TNM staging system, to which this database has been invited to contribute, is the development of a prognostic scoring system based on the outcomes of over 10,000 patients worldwide. This has the potential to shape the management of oesophageal cancer patients, particularly those who are unlikely to benefit from surgery. Such prognostic characteristics will be available to input on web-based and phone applications in real time, providing an immediate estimate of prognosis in a clinic setting. Whilst this is likely to be more sophisticated than other available predictive scores such as the Nottingham prognostic index for breast cancer, such scoring systems have been met with scepticism in some quarters. Whilst there will always be scope for decision-making based on an individual patient's wishes and a clinician's intuition, such a guide would undoubtedly be useful, particularly in justifying a non-operative approach.

Nowhere will individualised therapy become more prominent than in the field of oncology, where gene signatures and biological mapping of individual tumours will probably be commonplace in the future. Systemic therapy will target specific receptors using combinations of biological agents. The knowledge that a tumour expresses receptors for a given therapy will reduce the likelihood of a patients undergoing

systemic treatment for no benefit. Identifying patients who are not responding to treatment will still be critical as these patients may benefit from tumour re-profiling and second line therapy. Staging should incorporate anatomical and physiological assessments of the tumour both before and after chemotherapy, with best available evidence currently supporting the use of PET/CT. However MRI has shown some promise and has the potential to supersede CT in the future.

Overall, the role of surgery is likely to diminish. Early tumours will be treated by endoscopic therapy provided the long term results of this treatment show equivalent outcomes to surgery. As predictive models improve, particularly the ability to select patients with very poor forecasted survival following surgery, this group will probably be offered alternative oncological therapies. With more patients receiving definitive CRT, there is likely to be an increased demand for salvage resection in those patients with residual or recurrent disease.

The availability of tumour specific biological therapies will improve systemic treatment, such that only patients who have had prolonged and effective therapy will proceed to surgery. This may include patients who were initially deemed unsuitable for surgery, but become eligible courtesy of a good response to treatment. Whilst down-staging should prompt a re-evaluation of surgical options, prospective studies would need to verify the benefit of such an approach. The reduced morbidity and side-effect profile of biological agents, compared to chemotherapy, may allow for long term systemic treatment in a similar fashion to that employed for hormone receptor positive breast cancer or the use of Tyrosine Kinase inhibitors for gastro-intestinal stromal tumours. The morbidity and mortality associated with surgery, and the availability of alternative treatments, will inevitably drive further improvements in surgical standards and the centralisation of cancer surgery to fewer centres.

8.4 Conclusions

In conclusion, this thesis has shown in a large cohort of oesophageal resections that significant advances are being made in the investigation and treatment of these cancers. Outcomes are improving such that 5 year survival from surgery now approaches 50%. Nonetheless, 20% of patients fail to survive one year from surgery, highlighting the need to predict early recurrence and death. Most patients require neo-adjuvant therapy and current evidence supports the use of systemic chemotherapy as the first line treatment in patients with oesophageal adenocarcinoma. Arguably the two greatest challenges in this field are how to improve the efficacy of systemic therapy and the accurate measurement of tumour response to such treatment. The inevitable introduction of targeted therapies will change the landscape of oesophageal cancer management, such that the role of surgery in the future will need to be re-defined.

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Appendix

A.1 Study 1 protocol

Early recurrence and death after oesophageal cancer surgery

Background

Early recurrence and death after surgery for oesophageal cancer is a devastating outcome in which the magnitude of the surgery has not been justified by the duration of survival. Quality of life studies have demonstrated that the restoration of physical and emotional well-being takes at least 12-18 months from surgery. Therefore, a patient who dies within a year of surgery will not have re-gained their pre-operative quality of life before succumbing to their disease. If these patients could be identified prospectively, they could be offered alternative oncological therapies.

Aim

To compare a group of patients suffering ERD with a group of long-term survivors (>3 years from surgery) to identify the clinico-pathological characteristics associated with ERD.

Lead author : AD

Analysis / statistics : FM

Target journal : BJS

Methods

Red = Database column for selected parameter

Design: Cohort study based on the database of 680 patients (only those with malignant disease) – identified by Included in ERD study (Y) operated on at STH and RMH during the period 2000-2011 with follow-up until March 2012. Included are patients diagnosed with adenocarcinoma, adenosquamous and squamous cell carcinoma, and high grade dysplasia (HGD).

Groups are identified by ERD (ERD = 0; LTS = 1). ERD is calculated as survival of less than one year from date of surgery AND Recurrence (=Yes)

Main outcomes: 1. Odds ratio of presence in ERD group (rather than LTS) to identify factors associated with ERD

2. Patterns of recurrence

Survival outcomes on database

1. Patient is Dead or Alive (Dead (1) or Alive (0))

2. If dead, Date of death gives survival

3. If Alive, Date last seen gives survival

4. If dead with recurrence Outcome (Dead – distant mets, locoregional recurrence, locoregional recurrence & distant mets, complications of treatment all INCLUDED)

Multivariate model to include (Potential confounding factors):

1. Age at operation - DOB (Date of birth) (categorical)

2. Grade: HGD/CPR, Well, Moderate, or Poor

3. Tumour stage TNM (7th Ed)

(6 groups) – T0-2 N0, T0-2 N1, T0-2 N2-3, T3-4 N0, T3-4 N1, T3-4 N2/3

5. Chemotherapy response : Complete pathological response, Good OR partial response, Poor OR No response, Not applicable (i.e. no chemo given), not recorded (i.e. response unknown, chemo given)

6. Lymphovascular invasion: Yes or no

7. Resection type (R0/1/2): R0 (clear margins) vs R1/2 (R1 microscopic disease at margin OR R2 macroscopic disease)

8. Albumin (Albumin) <40, ≥40

9. CRP (CRP) <5, ≥5

Analysis (FM to do)

1. Multivariable model (crude and adjusted analysis) of the above clinic-pathological parameters to identify those associated with ERD. All patients and Adenocarcinoma sub-group (exclude SCC, adenosquamous) i.e. perform two runs of the model.

Other data we would like to have for the manuscript

1. Demographics

2. Oncology data (stage of disease, % having chemo, R0/1/2, LVI, chemo response etc)

3. In-hosp mortality – In hospital mortality (yes or no)

4. Hospital stay – Hospital LOS (continuous)

5. LN Yield – Total LNs (continuous)

6. CRM involvement – Radial margin positive (where CRM + = Yes OR <1mm ; CRM - = No)

7. Recurrence pattern – loco-regional, distant mets, locoregional AND distant mets ? Recurrence

Discussion themes

1. Can ERD be predicted (? Predictive modelling)
2. Comparison with Zhang study (SCC)

A.2 Study 2 protocol

The effect of the radicality of surgery on survival in oesophageal cancer

Background

The optimal surgical approach to oesophageal cancer is controversial. Some advocate radical surgery with two (or even three) stage procedures. However there is very limited evidence to suggest that this benefits patients when compared to the transhiatal approach, which typically is a less radical operation with limited possibilities for lymph node dissection in the chest. An advantage of the Transhiatal approach is the lower risk of pulmonary complications. The primary RCT that has compared the two approaches, showed no statistically significant differences in terms of overall survival, but greater morbidity in the transthoracic (2-stage) group [*Hulscher et al 2002*]. On sub-group analysis, there was a trend to long-term survival benefit in patients undergoing 2-Stage (radical) surgery in those with a low volume of positive lymph nodes.

Aim

To compare Transhiatal and 2-Stage procedures performed at STH and RMH over a ten year period to establish if there is any benefit to more radical surgery in terms of overall and disease free survival as primary outcomes.

Target journal : BJS, Annals of surgery

Methods

Red = Database column for selected parameter

Design: Cohort study based on the database of 665 patients (only those with malignant disease – I have identified these by Included in radicality study (Y) operated on at STH and RMH during the period 2000-2011 with follow-up until March 2012. Included are patients diagnosed with adenocarcinoma, adenosquamous and squamous cell carcinoma, and high grade dysplasia (HGD).

Exposures: We will compare Transhiatal (THO) to 2-Stage (2ST) procedures (THO or 2ST) regarding survival. THO includes all patients operated on with this procedure. 2ST includes the surgical procedures Ivor Lewis, Laparoscopic Ivor Lewis, MIO, and Left thoraco-abdominal (LTA).

Main outcomes:

1. Overall mortality within 5 years of surgery (or within period of follow-up if less than 5 years)

2. Disease-specific mortality (with documented tumour recurrence) within 5 years of surgery or period of follow-up if less than 5 years.

3. Disease free survival

Survival outcomes on database

1. Patient is Dead or Alive (Dead (1) or Alive (0))

2. If dead, Date of death gives survival

3. If Alive, Date last seen gives survival

4. If dead with recurrence Outcome (Dead – distant mets, locoregional recurrence, locoregional recurrence & distant mets, complications of treatment all INCLUDED)

Multivariate model to include (Potential confounding factors):

1. Age at operation - DOB (Date of birth) <60, 60-70, >70? (FM to decide cut-offs)

2. Grade: HGD/CPR, Well, Moderate, or Poor

3. Tumour stage TNM (7th Ed)

(6 groups) – Tis/HGD/T0, T1-2 N0, T1-2 N1-3, T3-4 N0, T3-4 N1, T3-4 N2/3

5. Chemotherapy response : Complete pathological response, Good OR partial response, Poor OR No response, Not applicable (i.e. no chemo given), not recorded (i.e. response unknown, chemo given)

6. Lymphovascular invasion: Yes or no

7. Surgical approach (THO or 2ST)

AND interchangeable with surgical approach (THO vs 2-ST) :-

8. Resection type (R0/1/2): R0 (clear margins) vs R1/2 (R1 microscopic disease at margin OR R2 macroscopic disease)

9. Lymph node yield (Total LNs) (0-9,10-19,20-29,>=30)

Analysis (FM to do)

1. Overall mortality - Include Surgical approach in a Cox regression multivariate model with other known prognostic factors to assess whether approach affects survival when these are taken into account. Possible confounders as above.

LN yield & Margin status (R0 vs R1/2) to replace surgical approach in 2nd run of model (This may demonstrate which of the two proposed mechanisms of difference is the most important)

2. Disease specific mortality – similar to above but using Recurrence Y/N (and date of recurrence rather than date of death)

LN yield & Margin status (R0 vs R1/2) to replace surgical approach in 2nd run of model

Other data we would like to have for the manuscript

1. Demographics

2. Oncology data (stage of disease, % having chemo, R0/1/2, LVI, chemo response etc)

3. In-hosp mortality – (THO vs 2ST) In hospital mortality (yes or no)

4. Hosp stay – comparison of means/medians (THO vs 2ST) Hospital LOS (continuous)

5. LN Yield – comparison of means / medians Total LNs (continuous)

6. CRM involvement –THO / 2ST vs CRM + / CRM – Radial margin positive (where CRM + = Yes OR <1mm ; CRM - = No)

7. Recurrence pattern – THO / 2ST vs loco-regional, distant mets, locoregional AND distant mets ? Recurrence

8. Survival analysis stratified by T stage, N stage (N0-3), tumour location (oes/type 1, type 2)

Additional proposal :-

1. The world oes CA collaboration recently published guidelines for adequacy of lymphadenectomy based on T stage. I am interested to know if increased Lymph node yield in itself gives a prognostic advantage (they suggest it does).

2. In terms of radicality I think you can argue that 2ST may provide two theoretical advantages

   A. Greater Lymphadenectomy

   B. Removal of peri-oesophageal tissue thus reducing your CRM (R1) rate

That is why I felt we should look at these two features separately to see if surgical approach affects these. It almost certainly will affect A….. B will be interesting

I propose we run the Adjusted model twice :-

(i). Age, stage, grade, Chemo response, Lymphovascular invasion, Surgical approach (THO vs 2-Stage) (ie EXCLUDE MARGIN STATUS and LN yield as this may be affected by surgical approach which is already in the model)

(ii). Age, stage, grade, Chemo response, Lymphovascular invasion, Margin status, Lymph node Yield (ie take surgical approach OUT of model and replace it with Margin status and LN yield)

2. We need to do further analysis by tumour location e.g. Oes/Type I/ Type II. There is some evidence that a THO may be as good as 2ST for Junctional tumours but not as effective for true oesophageal / Type 1. We should therefore stratify according to tumour location and tumour stage in a separate analysis.

If we do the above we could reasonably draw conclusions on :

1. Whether 2-Stage resection confers an advantage over Transhiatal surgery in terms of overall survival, and disease free survival (Adjusted model)

2. Whether a subset of patients may be better served by more radical surgery (as previously suggested in the RCT) (stratified analysis) (T1/2, T3/4, N0, N1, N2, N3, Oes, Type 1 OGJ, Type 2 OGJ)

3. How the two approaches compare in terms of Hosp stay, In hospital mortality, LN yield, Margin status and Recurrence pattern (simple statistics)

Ref

Hulscher, J.B., et al., *Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus.* N Engl J Med, 2002. **347**(21): p. 1662-9.

A.3 Study 3 protocol

Tumour down-staging after neo-adjuvant chemotherapy determines survival in adenocarcinoma of the oesophagus and oesophago-gastric junction

Introduction

Neo-adjuvant chemotherapy has become established in the treatment of oesophageal cancer in the UK following a survival benefit demonstrated in three high profile randomised controlled trials (OEO-2, MAGIC, FFCD). However, the effects of down-staging following chemotherapy are poorly understood and the ability to quantify this benefit remains elusive.

The assumption that systemic chemotherapy may have the ability to eradicate micro-metastases is one of the arguments for this strategy over and above neo-adjuvant chemo-radiation. Additionally, the relative importance of tumour stage before and after chemotherapy is unknown.

Hypotheses

1. Down-staging by neo-adjuvant chemotherapy results in a survival benefit
2. This survival benefit is manifest by improved local AND systemic control
3. Staging after chemotherapy is more important prognostically than initial staging

Target journals : Lancet Oncology, JCO

Statistical analysis (FM to do)

1. Survival (KM) analysis examining stage before and after chemotherapy (T0N0, T1-2 N-, T1-2 N+, T3-4 N-, T3-4 N+)
2. Compare down-staged patients and non-downstaged patients in terms of pathological response (Mandard score), Local recurrence and systemic recurrence
3. Multivariate model, utilising Downstaged Y/N (study exposure), adjusted for known confounding factors (patient age, tumour grade, lympho-vascular invasion, clinical stage). Outcome measures – overall survival, disease free survival
4. Correlation between Tumour Downstaged (Y/N) and Chemotherapy response i.e. Mandard scores (Complete/good/moderate/poor/no response).

Database parameters for multivariable model (#3)

Patients to be included in study :- Included in chemo study = Y
Study exposure :- Downstaged after chemo (Y/N)

Confounders :-

Age at operation (continuous)
Pre-op stage (T0N0; T1-2 N-; T1-2 N+; T3-4 N-; T3-4 N+)
Grade (well/moderately/poorly differentiated)
Lymphovascular invasion (Y/N)

Figures/Tables

Table 1 – Demographics / oncological data
Table 2 – Multivariable model
Figure 1 – 4 KM survival curves (down-staged vs non-down-staged vs “control”)

Outcome :-

Time to death (Overall survival) Date of death

Time to recurrence (Disease free survival) Date of recurrent disease

Discussion

Tumour behaviour – stage before vs stage after NAC

Recurrence patterns – local /systemic effect or both. Compare with CRT ?

Importance of down-staging compared to other prognostic factors

Implications for staging